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Neural Modeling and Functional Brain Imaging: An Overview

Barry Horwitz
Brain Imaging & Modeling Section
NIDCD, NIH

Methods to Understand Neural Basis of Human Cognition

1. Brain lesions & cognitive neuropsychology
2. Electrophysiological recordings in primates (mammals)
3. Pharmacological and genetic studies
4. Transcranial magnetic stimulation
5. Functional neuroimaging

   Hemodynamic-metabolic methods (PET, fMRI)
   Electric-magnetic methods (ERP, MEG)

All these data are generally incommensurate with one another.

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Functional neuroimaging enables the activity of all brain regions to be seen simultaneously – hence, network analysis becomes necessary.

Functional Neuroimaging Methods

- Two-dimensional surface imaging
  (e.g., 133-Xenon inhalation method)
- Optical imaging
- Single photon emission computed tomography
  (SPECT)
- Positron emission tomography (PET)
- Functional magnetic resonance imaging (fMRI)
- Evoked potentials, electroencephalography (ERP,EEG)
- Magnetoencephalography (MEG)

Functional Neuroimaging Methods

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- Transcranial magnetic stimulation (TMS)

17th Century anonymous engraving. The Physician Curing Fantasy. By permission, Philadelphia Museum of Art.

Relation of Brain Functional Activity to Cerebral Blood Flow

Brain functional activity

↓

Cellular work

↓

Cerebral oxidative metabolism

↓

Delivery of oxygen and glucose

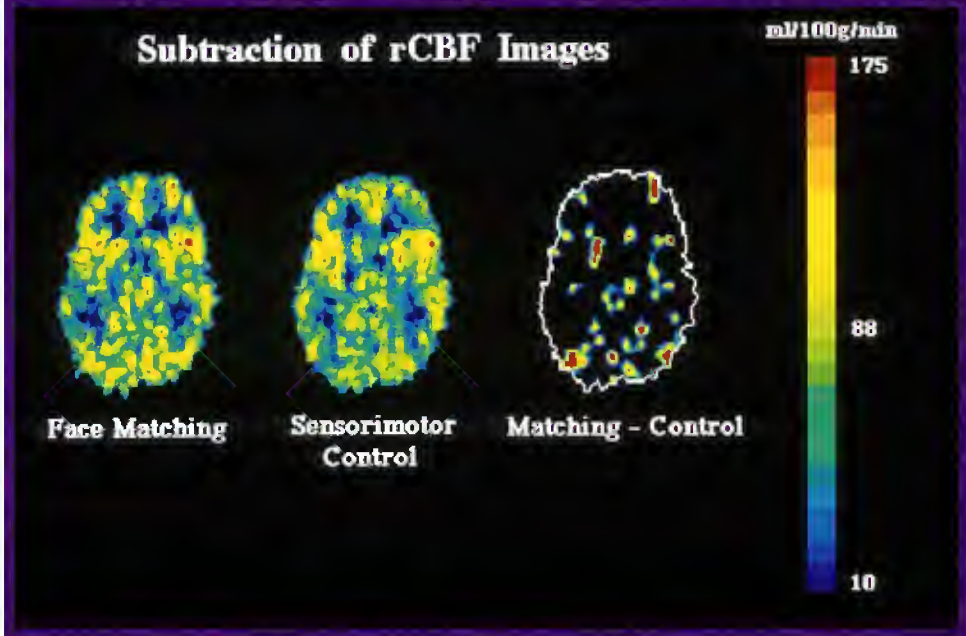
↓

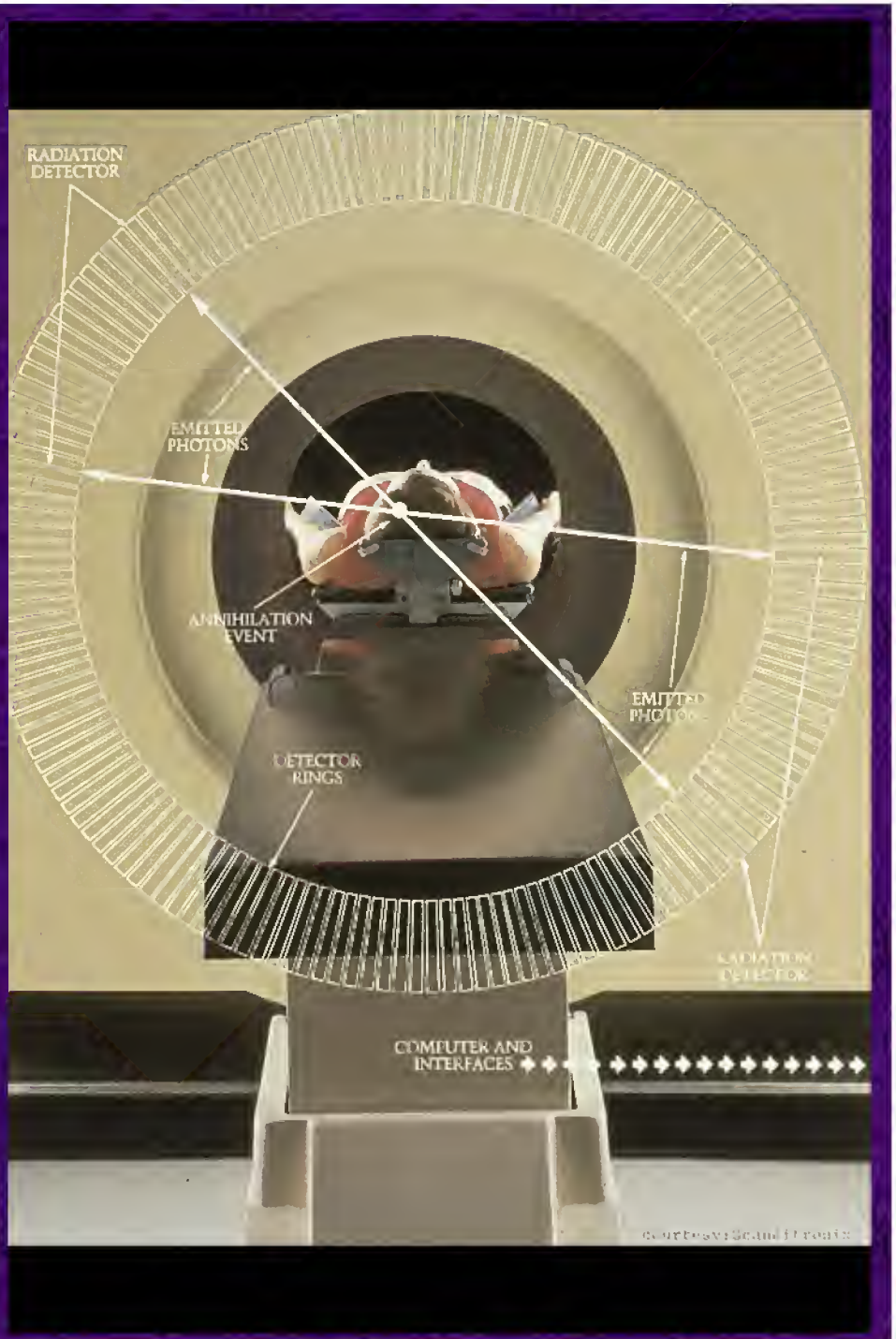
Cerebral blood flow (CBF)

Characteristics: Functional Neuroimaging Methods

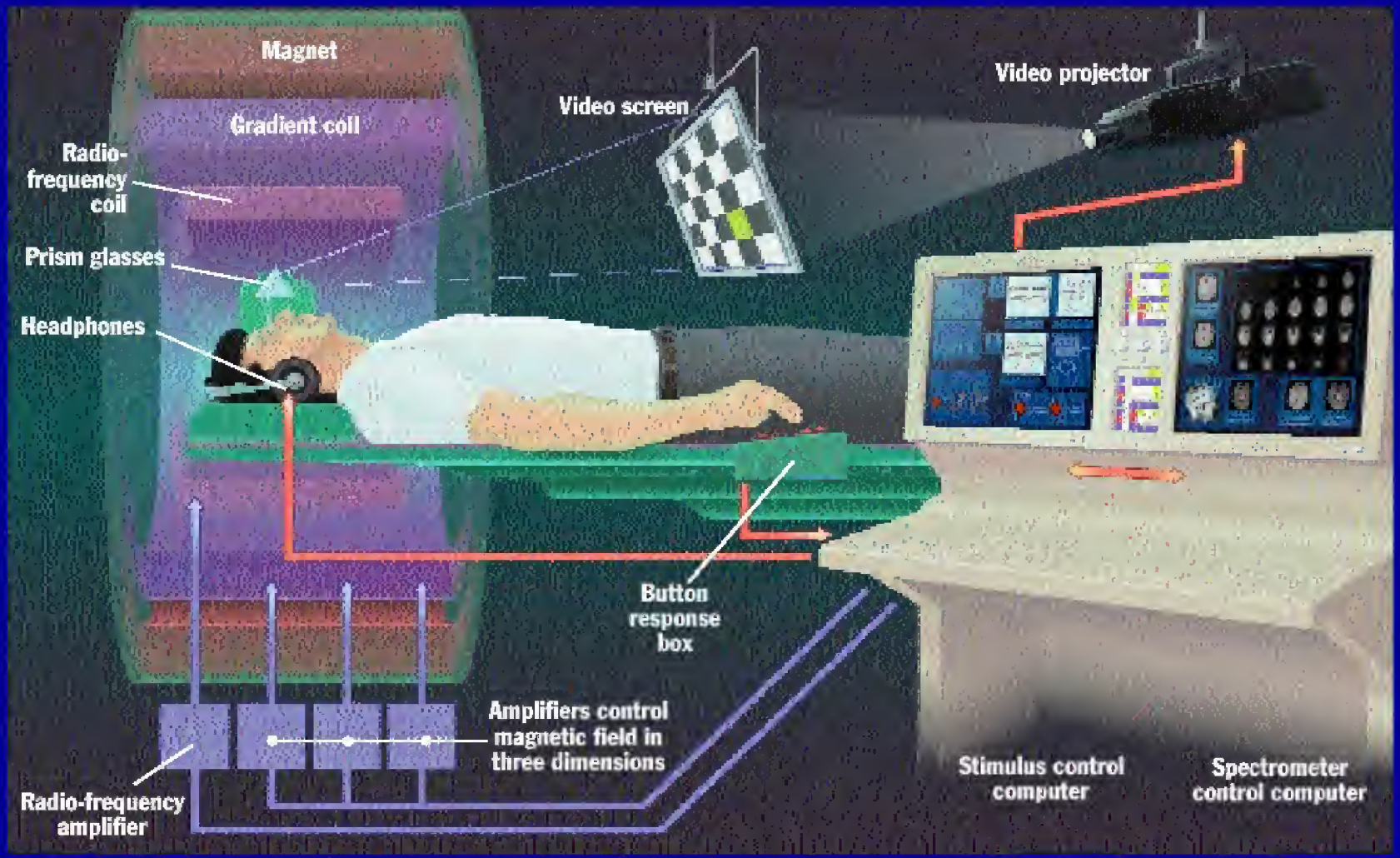
Technique	Variable	Time Resol.	Spatial Resol.	Comments
2D-Surface Imaging	133-Xe rCBF	5-7 min	2.5 cm	nontomographic no deep structures 3 runs
SPECT	99m-Tc-HMPAO/rCBF	1-2 min	7 mm	semiquant.;2 runs
	99m-Tc-ECD/rCBF	1-2 min	7 mm	2 runs
	133-Xe/rCBF	2 min	7 mm	3 runs
PET	[15-O]water/rCBF	15 sec-1 min	5 mm	multiple runs
	[18-F]FDG/rCMRglc	15-30 min	5 mm	1 run
ERP	scalp-recorded electric potetial	1 msec	Very coarse	many trials
MEG	magnetic field/ current source	1 msec	A few mm	many trials nonunique soln.
fMRI	blood oxygenation	A few sec.	2 mm	many runs semiquant. source of signal

Positron Emission Tomography



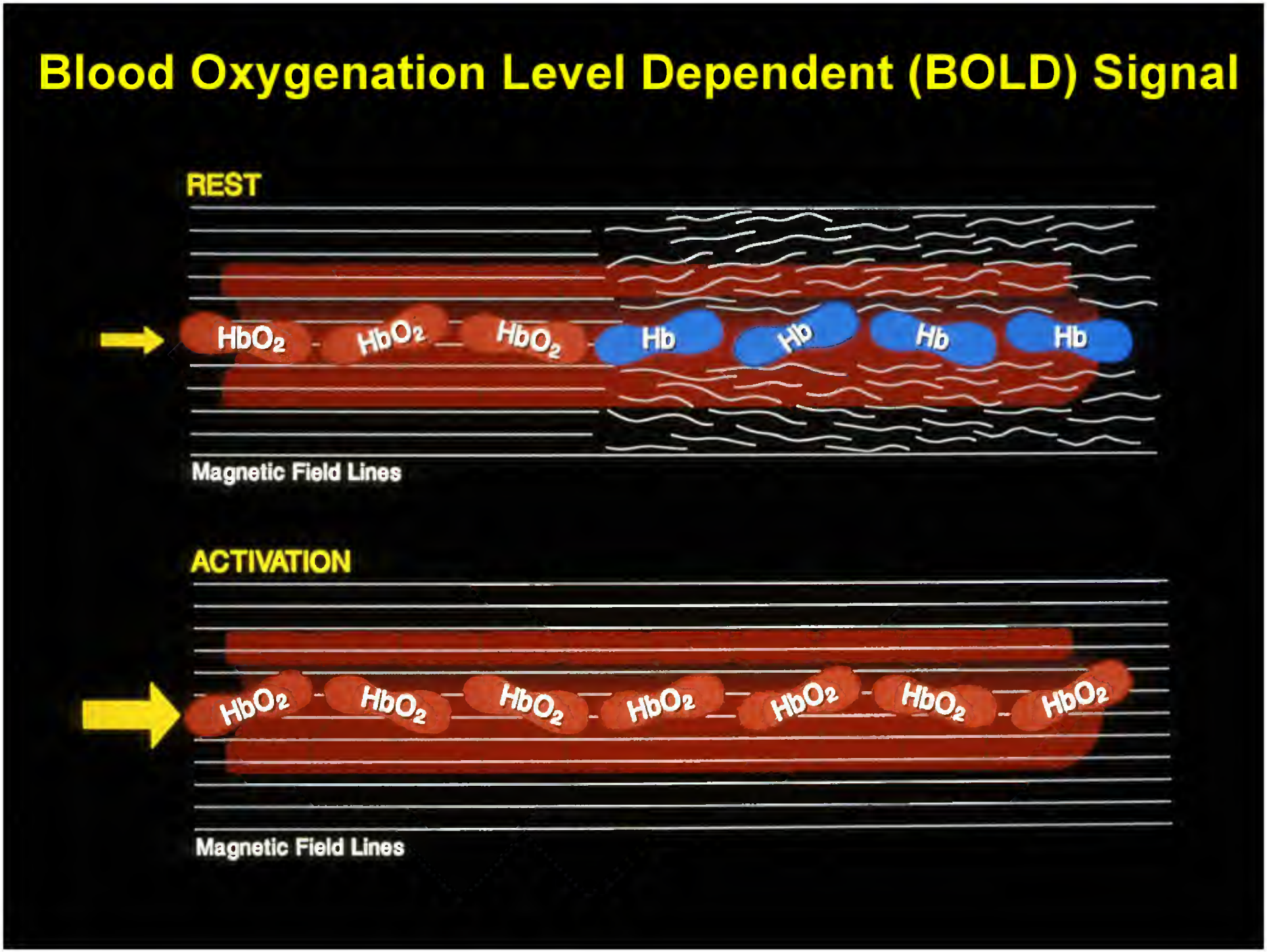


fMRI Setup

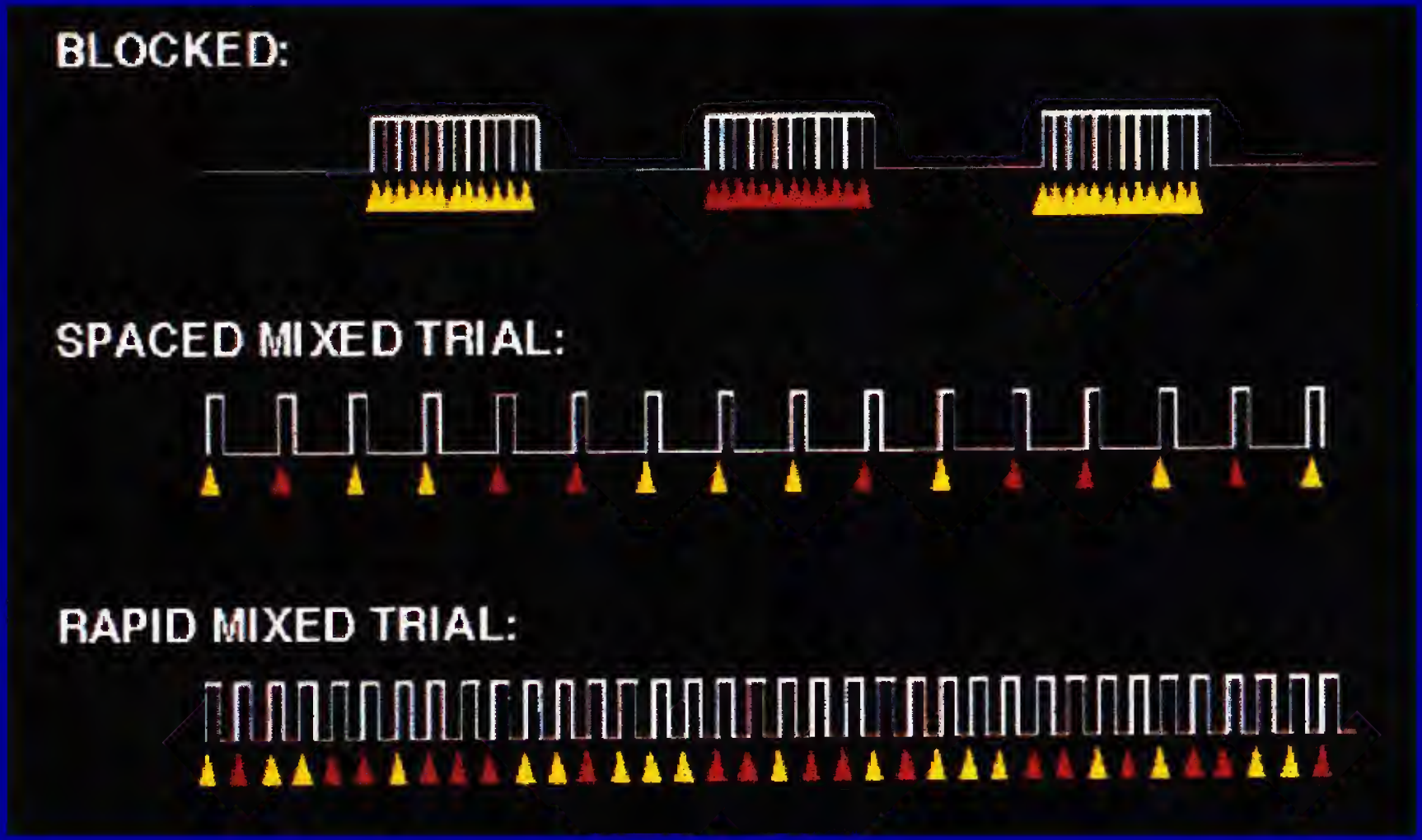


Jody Culham – fMRI Course (http://defiant.ssc.uwo.ca/Jody_web/courses.htm)

Blood Oxygenation Level Dependent (BOLD) Signal



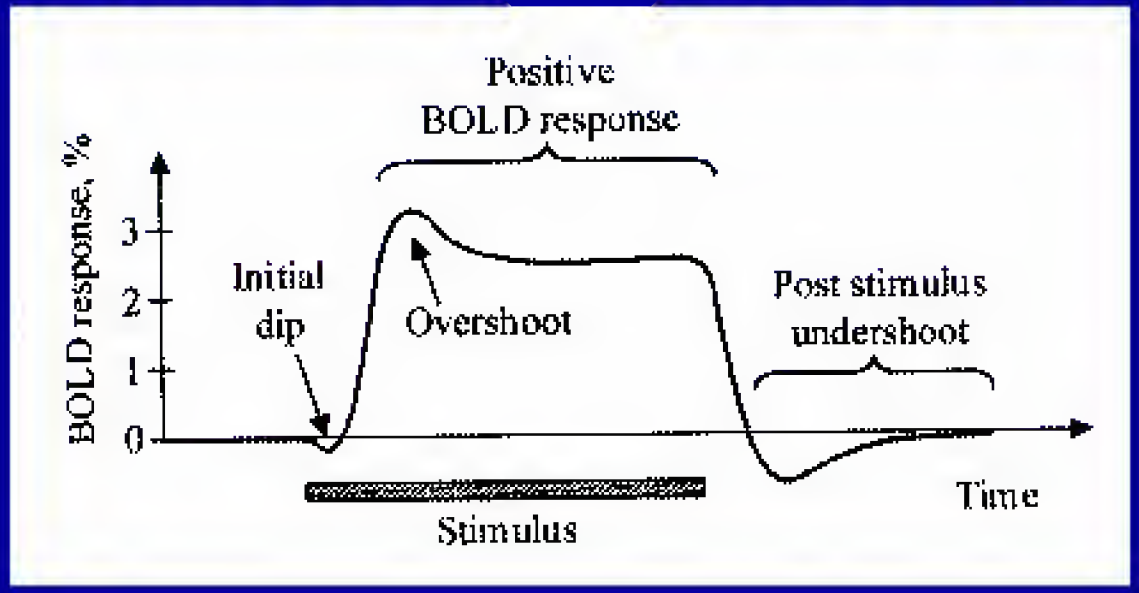
Blocked vs. Event-related



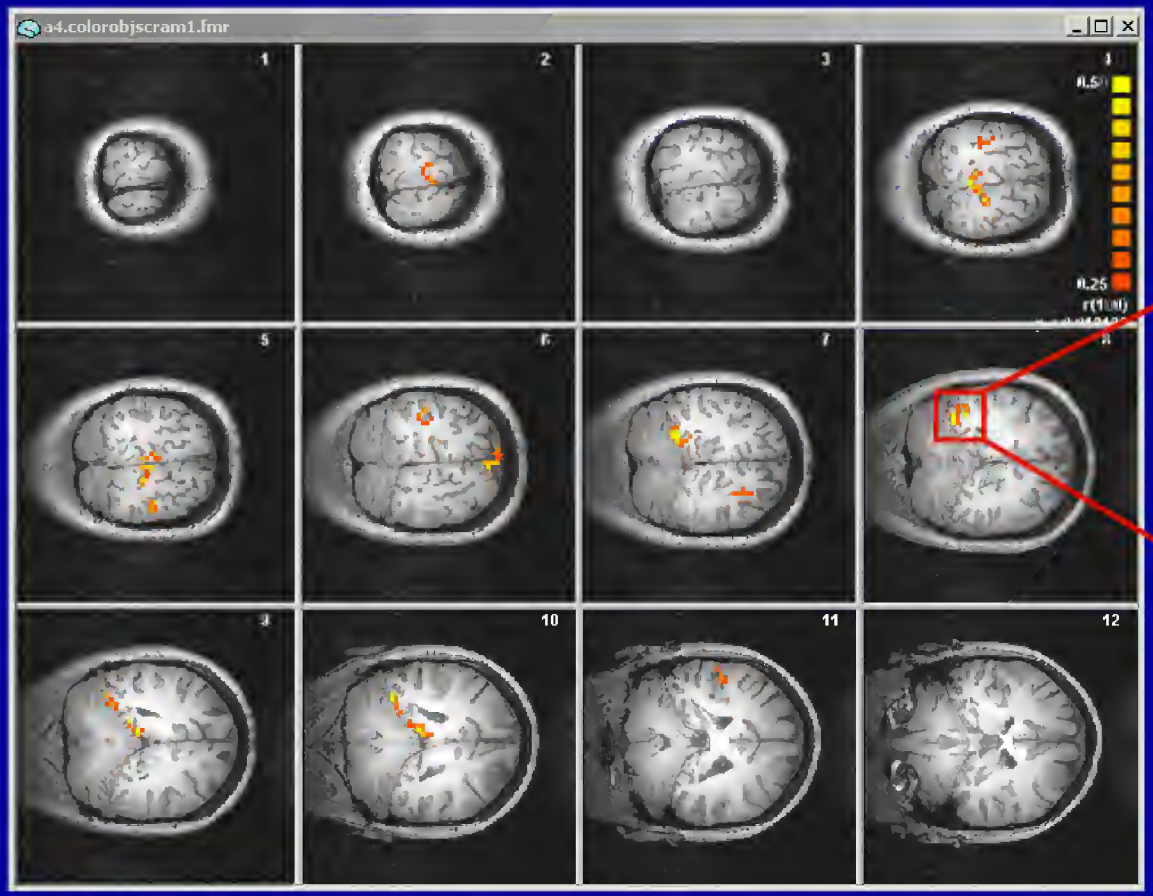
Source: Buckner 1996

Block Designs

Assumption: Because the hemodynamic response delays and blurs the response to activation, the temporal resolution of fMRI is limited.

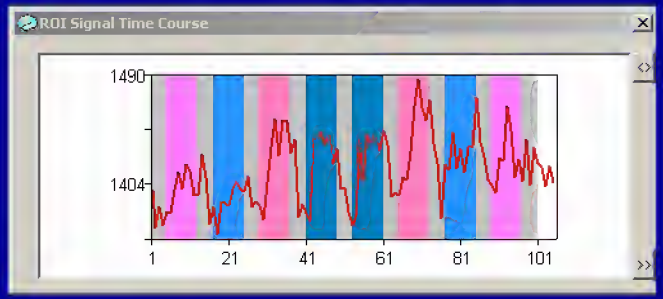


Statistical Maps & Time Courses



Use stat maps to pick regions

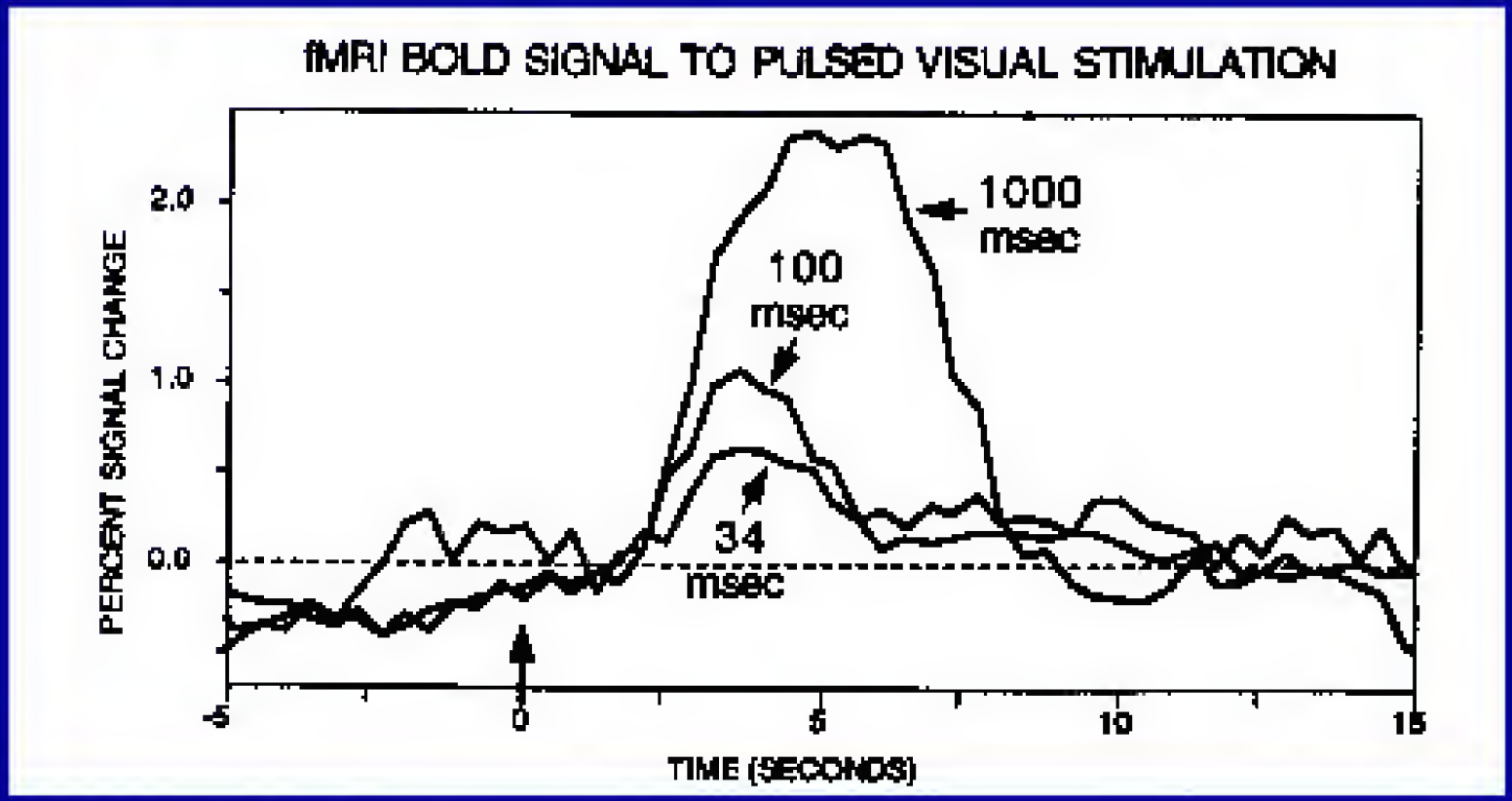
Then extract the time course



What are the temporal limits?

What is the briefest stimulus that fMRI can detect?

- Blamire et al. (1992) – 2 sec
- Bandettini (1993): 0.5 sec
- Savoy et al (1995): 34 msec



MEG Study of Visual Word Processing

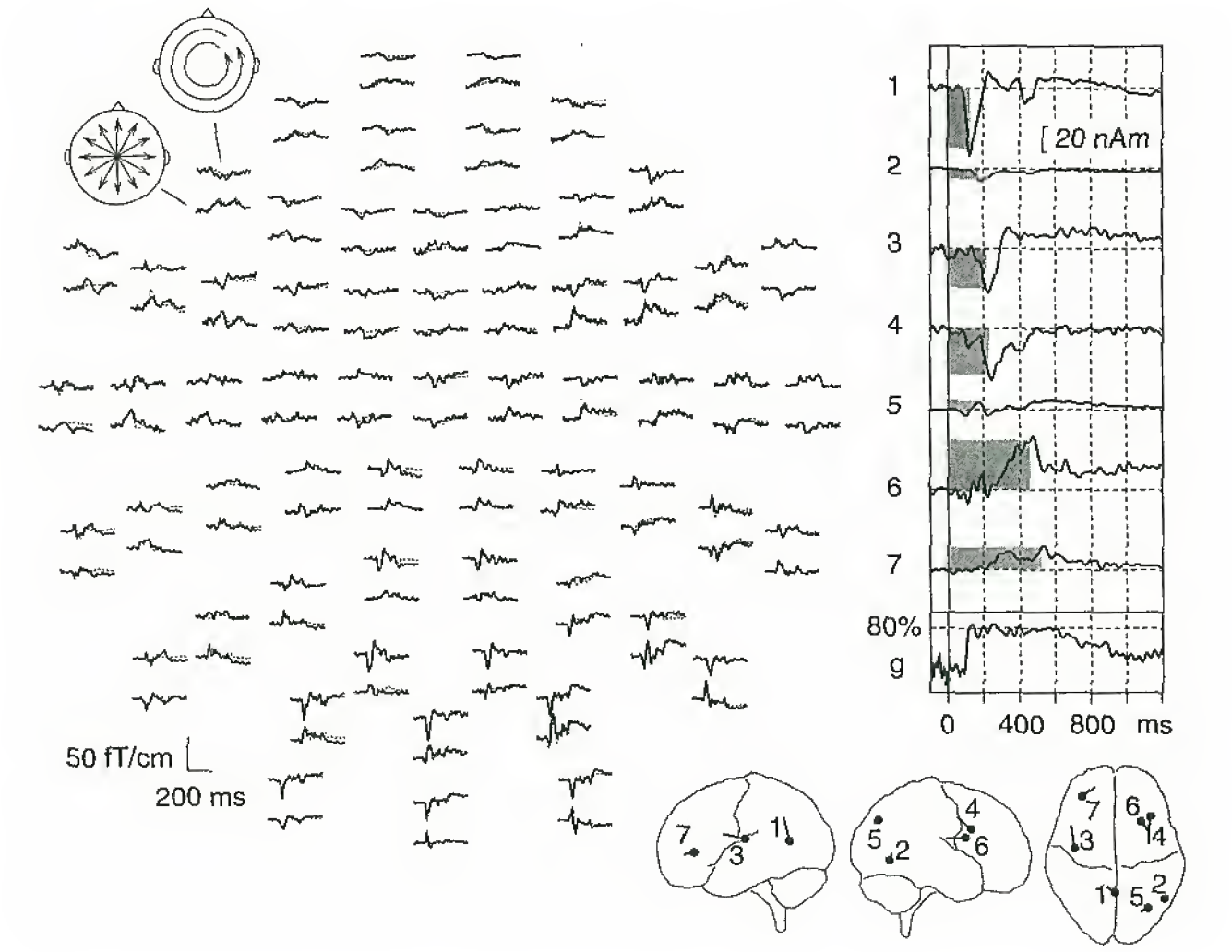


Figure 3

Acquiring and Interpreting the Signal

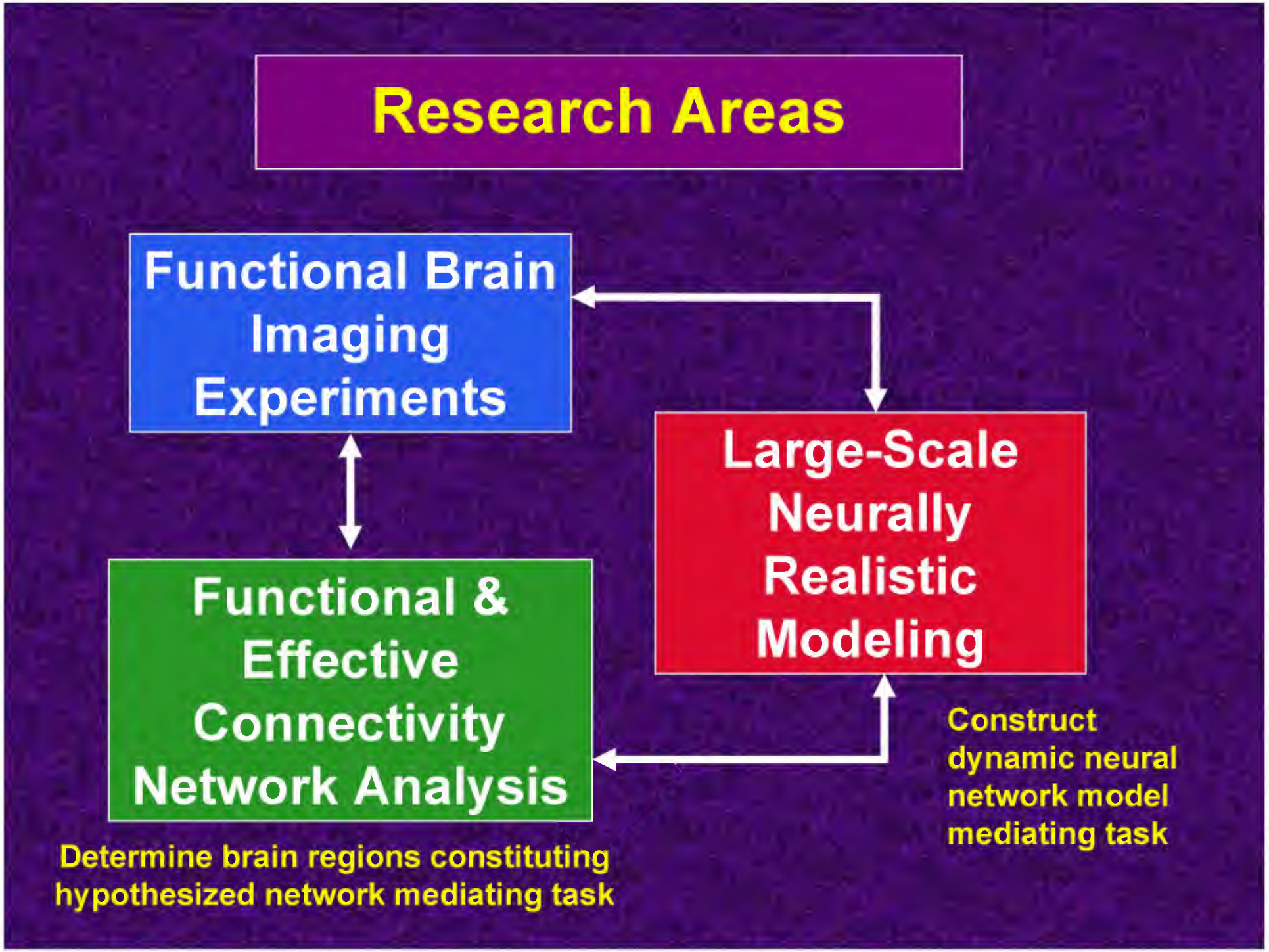
*1. Relation of neural activity to the variable that is to be imaged (e.g., rCBF, blood oxygenation).
2. Relation of the imaged variable to the the signal (e.g., brain radioactivity, intensity in T2*-sensitized images).
3. Physics of measuring device (e.g., photodetectors, RF coils).
4. Hemodynamics/metabolism of labeled quantity (e.g., [18-F]FDG, oxygenated hemoglobin).
5. Paradigm design.
6. Statistical analysis of image.
*7. Interpreting the results in terms of neurobiology/cognitive neuroscience.

Neurobiological Substrate of Functional Neuroimaging Signals

- What is the relation between neuronal activity (ion flux) and vascular/metabolic response? Some information will come from from optical imaging studies, some from fMRI analyses, some from nonhuman animal rCBF experiments.
- Need to scale up this relation to the level of a cortical column or other well-defined anatomical structure. Need to determine the role neuromodulatory transmitters (e.g., ACh, 5HT, etc.) play in regulating rCBF.
- This method was used to understand some information about the neurobiological source of ERP.
- One then can use modeling to assess the importance of the firing of various synaptic populations on the functional neuroimaging signal.

Some questions That Computational Neuroscientistists Can Address With Respect To Functional Neuroimaging

- Biological Substrates of Neuroimaging Signals
- Relation of Dynamic Measures of Functional Activity (e.g., MEG) to "Steady-State" Measures (e.g., PET)*
- Systems-Level (Network) Modeling
- Relation of Systems-Level Models to Neuronal, Ensemble and Cognitive Models


Research Areas
Functional Brain Imaging Experiments
Large-Scale Neurally Realistic Modeling
Functional & Effective Connectivity Network Analysis
Construct dynamic neural network model mediating task
Determine brain regions constituting hypothesized network mediating task

PET/fMRI Data Analysis Strategies

Subtraction paradigm (Functional Segregation)

Task changes neural activity in a region.

Compare task with control task to find brain regions used by task.

Covariance paradigm (Functional Integration)

Task is mediated by a set of interacting brain regions.

Regions whose activities are correlated are part of neural network mediating task.

Broca's Area and Language Production

Broca's area

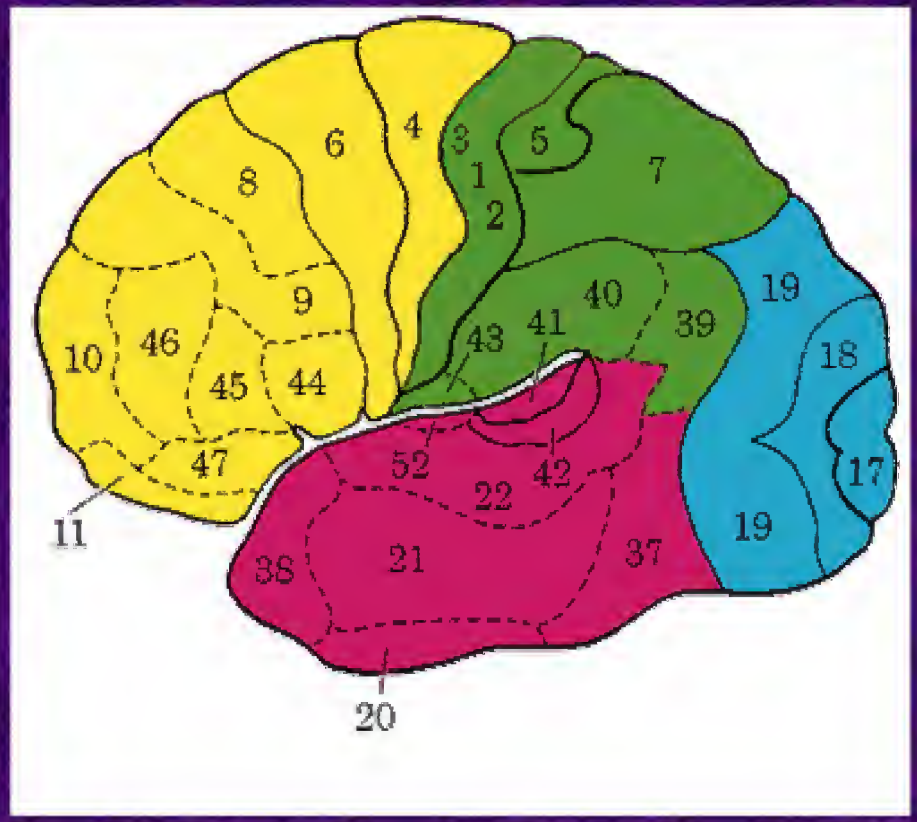
- Left inferior frontal gyrus (LIFG)
- Lesions result in a language production deficit
- Not well defined - many tasks activate this part of LIFG
- Braun et al. (Brain, 2001) used PET to study speech and ASL

Cytoarchitectonics

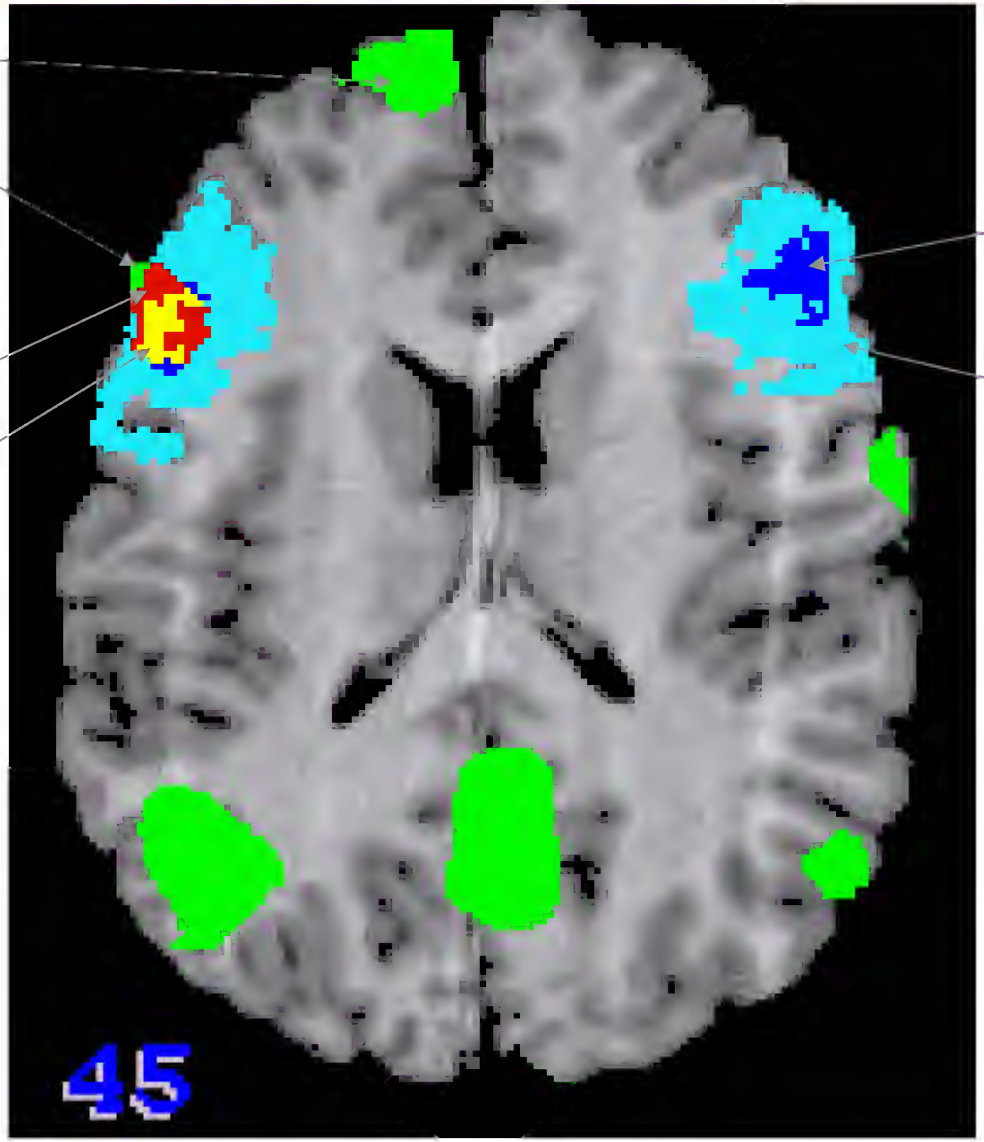
- Layering of neurons in the 6 cortical layers
- Brodmann areas
- Probabilistic brain atlas

Questions

- Do speech and ASL activate Broca's area (BA44 and BA45)?
- Is Broca's area activated by nonlanguage tasks?

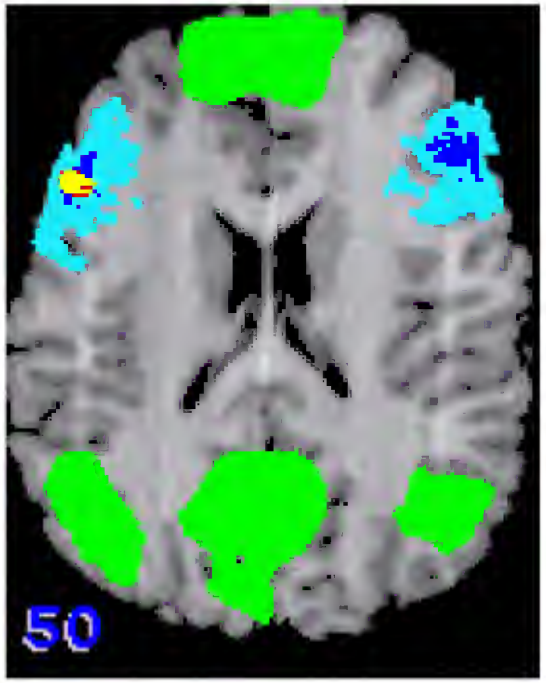


Probabilistic Brain Atlas

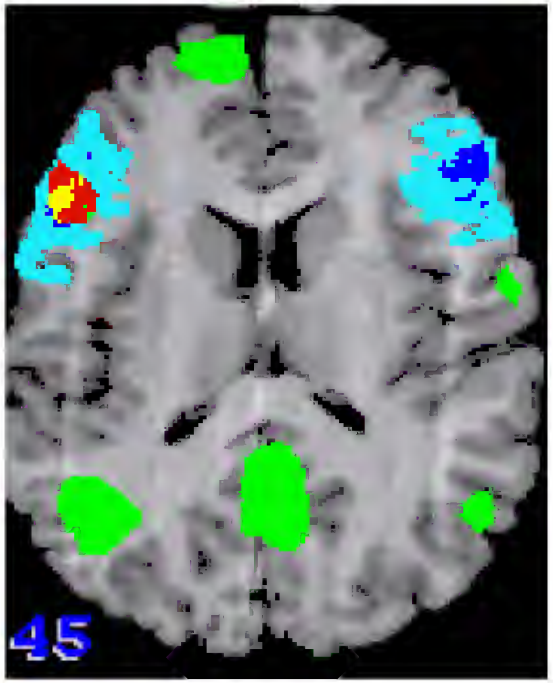


Brodmann Area 45 and Language Production

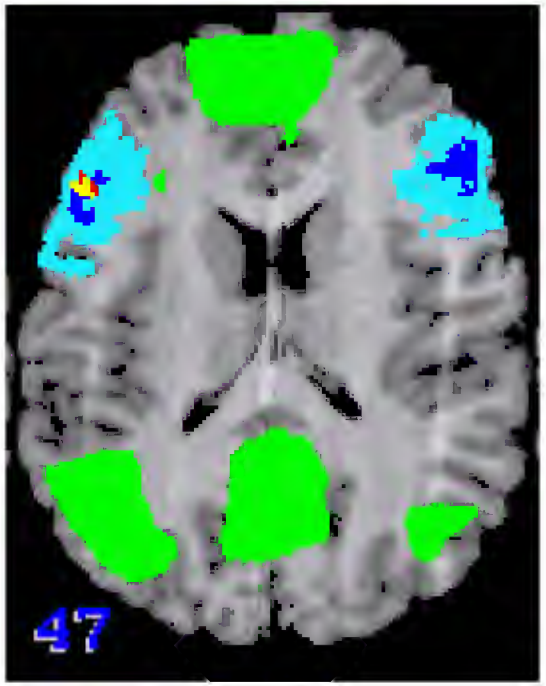
L



SPEECH vs.
MOTOR Control



ASL vs. LIMB
Control



SPEECH vs.
MOTOR Control
Monolinguals

R

Conclusions:

1. **Similar neural substrates in BA45 are used by ASL and Speech.**
2. **Non-language tasks can activate BA44 (not shown).**

Functional Connectivity

Interregional functional connectivity is evaluated as the correlation coefficient

(1) between subject-to-subject activities for PET

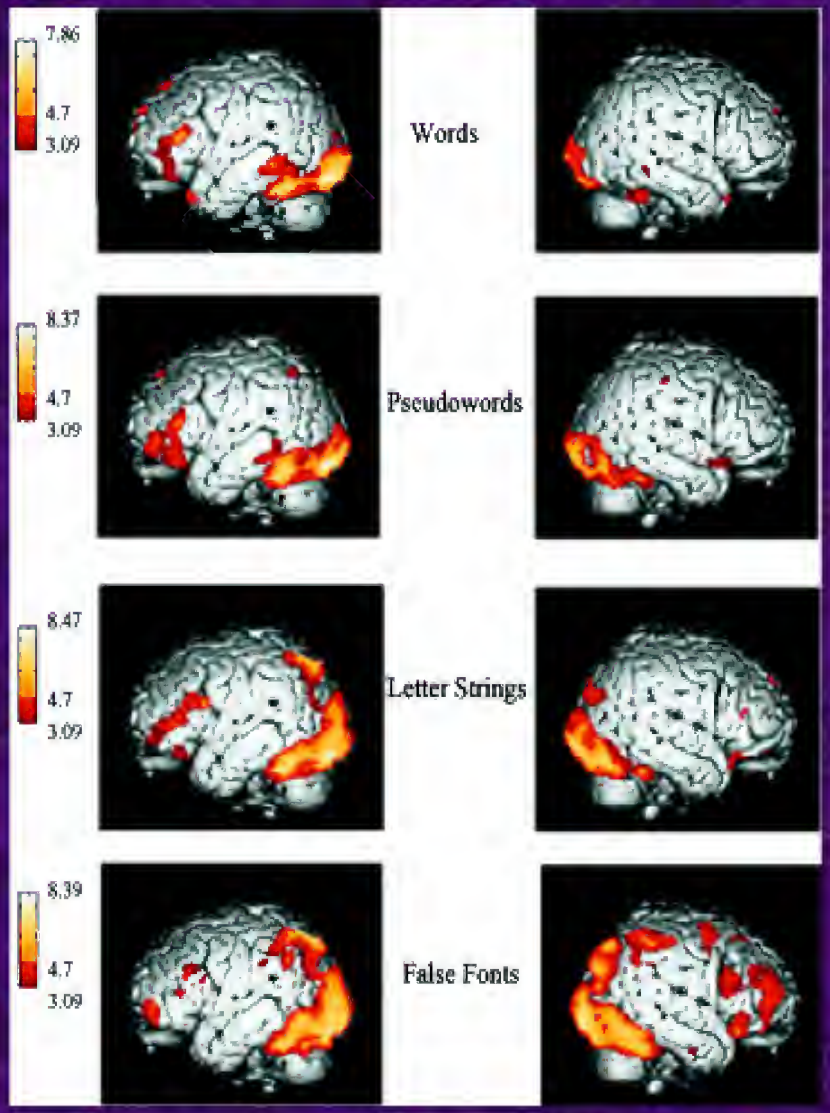
or

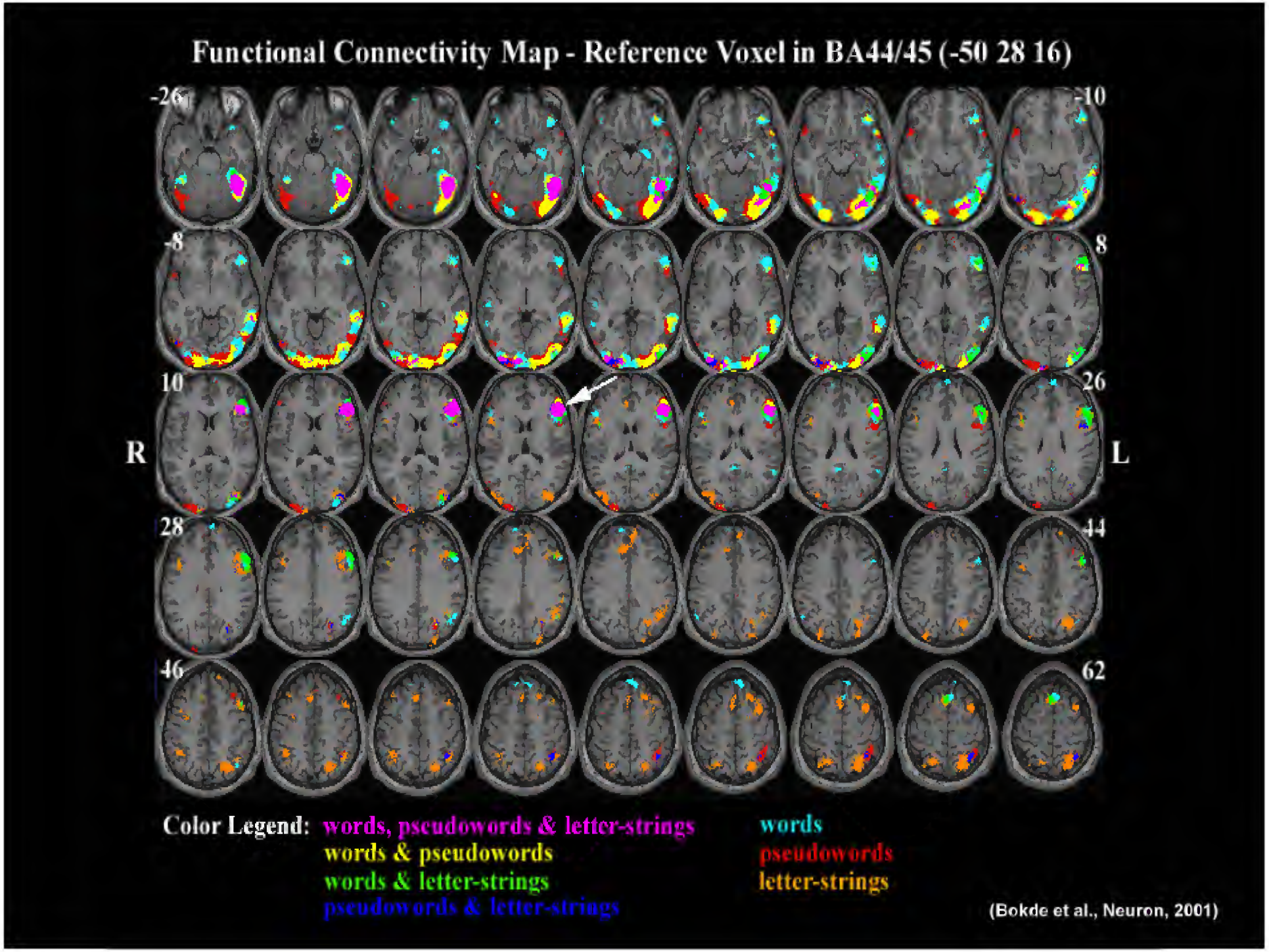
(2) between interregional time-series activities for fMRI.

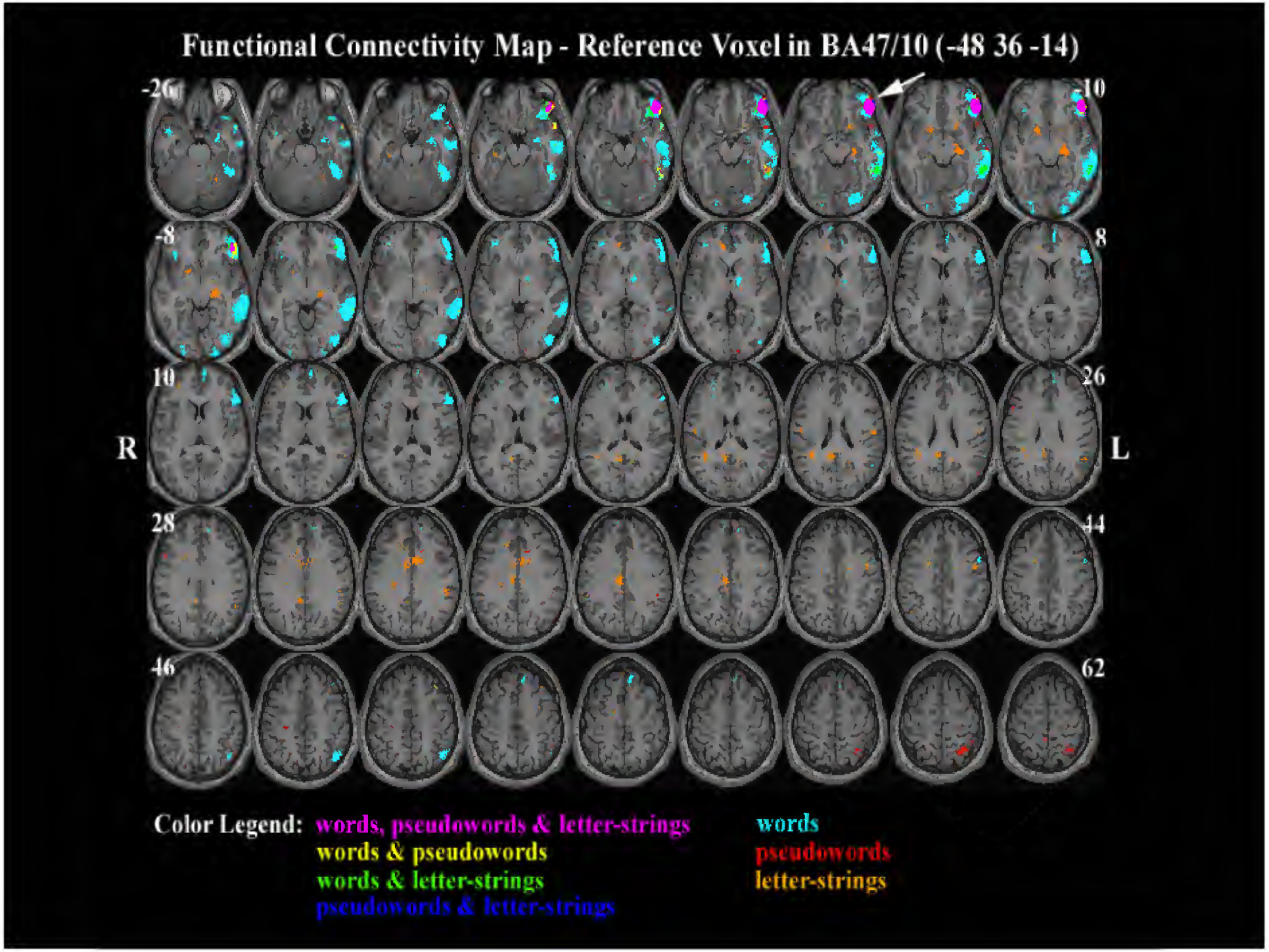
(Horwitz et al., PNAS, 1998)

Results -- Subtraction Paradigm

- Tagamets et al. (J. Cogn. Neurosci., 2000), using SPM, found a shift in the pattern of activity in going from words to pseudowords to letter strings to false fonts.
  - Lateralization changes
    - left to bilateral in posterior cortex
    - left to right in frontal cortex
  - Increased recruitment of parietal cortex
  - Decreased activity in left post. temp. cortex
- The above changes reflect shifts in the semantic and phonological content of the stimuli.




Functional Connectivity Map - Reference Voxel in BA44/45 (-50 28 16)
-26
-10
-8
8
10
26
R
L
28
44
46
62
Color Legend:
words, pseudowords & letter-strings
words & pseudowords
words & letter-strings
pseudowords & letter-strings
words
pseudowords
letter-strings
(Bokde et al., Neuron, 2001)


Functional Connectivity Map - Reference Voxel in BA47/10 (-48 36 -14)
-26
-10
-8
8
10
26
R
L
28
44
46
62
Color Legend:
words, pseudowords & letter-strings
words & pseudowords
words & letter-strings
pseudowords & letter-strings
words
pseudowords
letter-strings

Brain Connectivity

Anatomical Connectivity

Functional Connectivity

Effective Connectivity

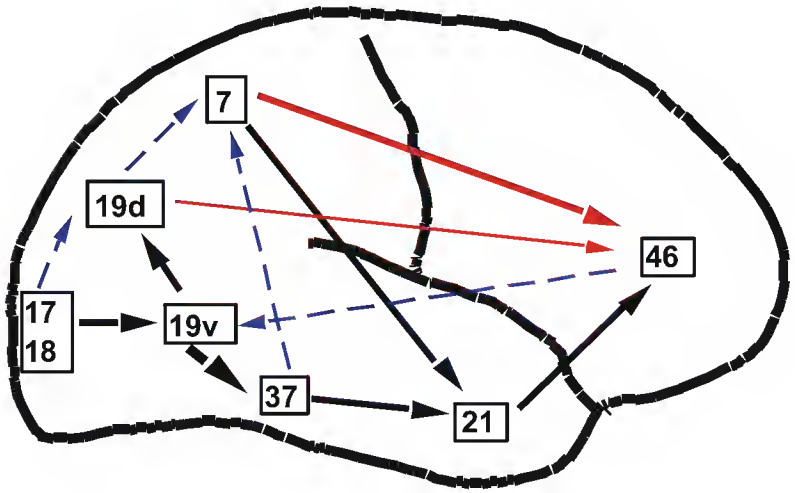
Systems-Level Network Analysis
(Structural Equation Modeling or Path Analysis)

Correlations between regions may be due to both direct and indirect effects.

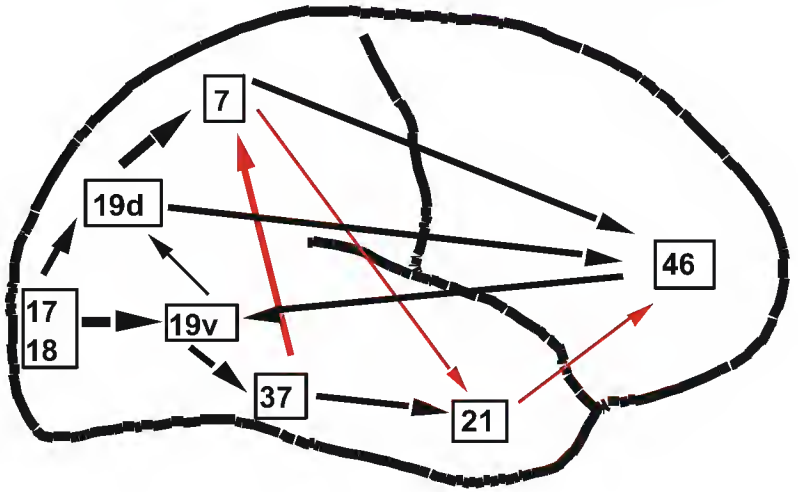
- **Goal:** account for the observed correlations between all regions of interest in terms of the known functional linkages (path coefficients) between these regions.
- **Starting point:** covariance or correlation matrix between activity in each region of interest, along with the anatomical connections between these regions.
- **Method:** functional strengths of these linkages are adjusted until calculated and observed correlation matrices are as identical as possible.
- **Result:** functional systems-level neural model corresponding to the task of interest.

Path Analysis Models for Face and Dot-Location Matching

Face Matching



Dot-Location Matching



Path Coefficients

Positive

0.7 to 1.0

0.4 to 0.6

0.1 to 0.3

Negative

-0.7 to -1.0

-0.4 to -0.6

-0.1 to -0.3

0

McIntosh et al., J. Neuroscience, 1994

Problems with Relating Hemodynamic Data to Underlying Neural Activity

1. **Spatial resolution** - each PET or fMRI resolvable element contains multiple and diverse neuronal populations.

2. **Temporal resolution** - temporal resolution of neuronal activity is on the order of milliseconds; PET and fMRI (because of hemodynamic delay) is on the order of seconds; fast transients may be invisible to PET/fMRI.

3. **Synaptic vs. neuronal activity** - electrical activity comes from cell body firings, PET/fMRI reflect primarily the activity of synapses; excitatory vs. inhibitory.

4. **Connectivity** - PET/fMRI activity is a mixture of local and afferent synaptic activity.

Large-Scale Neural Modeling

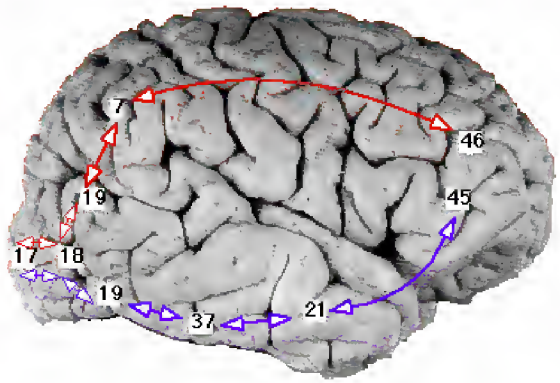
Goal: Construct a large-scale, neurobiologically realistic neural model that can perform tasks like those studied by PET and fMRI.

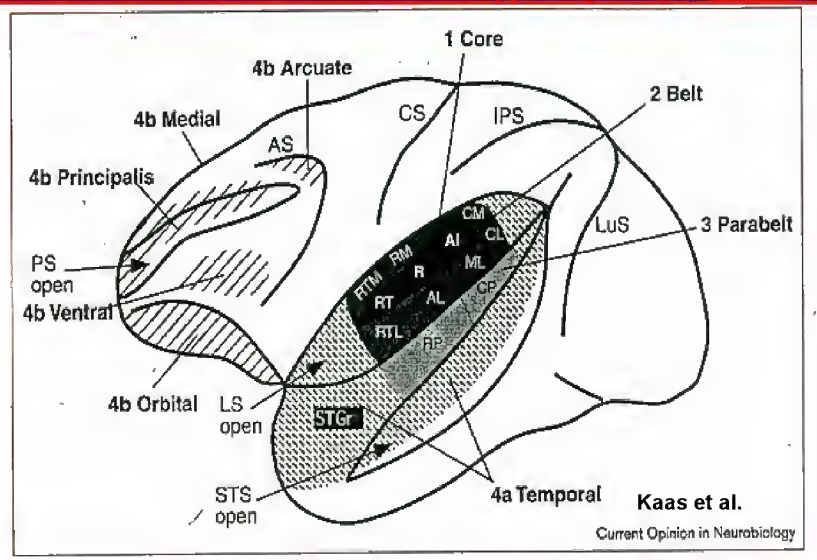
- Multiple, interconnected brain regions (feedforward and feedback connections).
- Each region consists of multiple neuronal units (cortical column).
- The basic unit consists of an excitatory-inhibitory pair.
- Model can perform multiple tasks (e.g., DMS for shape, control task).
- Dynamic behavior of excitatory units in each region matches that observed by primate electrophysiological studies.
- Synaptic activity (both excitatory and inhibitory), integrated spatially and temporally, represents rCBF/BOLD.

Large-Scale Neural Modeling

- Visual Delayed-Match to Sample for Shape (Visual Object Processing): PET and fMRI (Tagamets & Horwitz, Cerebral Cortex, 1998; Horwitz & Tagamets, HBM, 1999)
- Transcranial Magnetic Stimulation (TMS) and PET (Husain et al., NeuroImage, 2002)
- Inhibition and PET/fMRI Activity (Tagamets & Horwitz, Brain Res. Bull., 2001)
- Auditory Delayed Match-to-Sample for Tonal Patterns (Auditory Object Processing)
- Perceptual Grouping for Auditory Objects
- Functional Connectivity: PET and fMRI

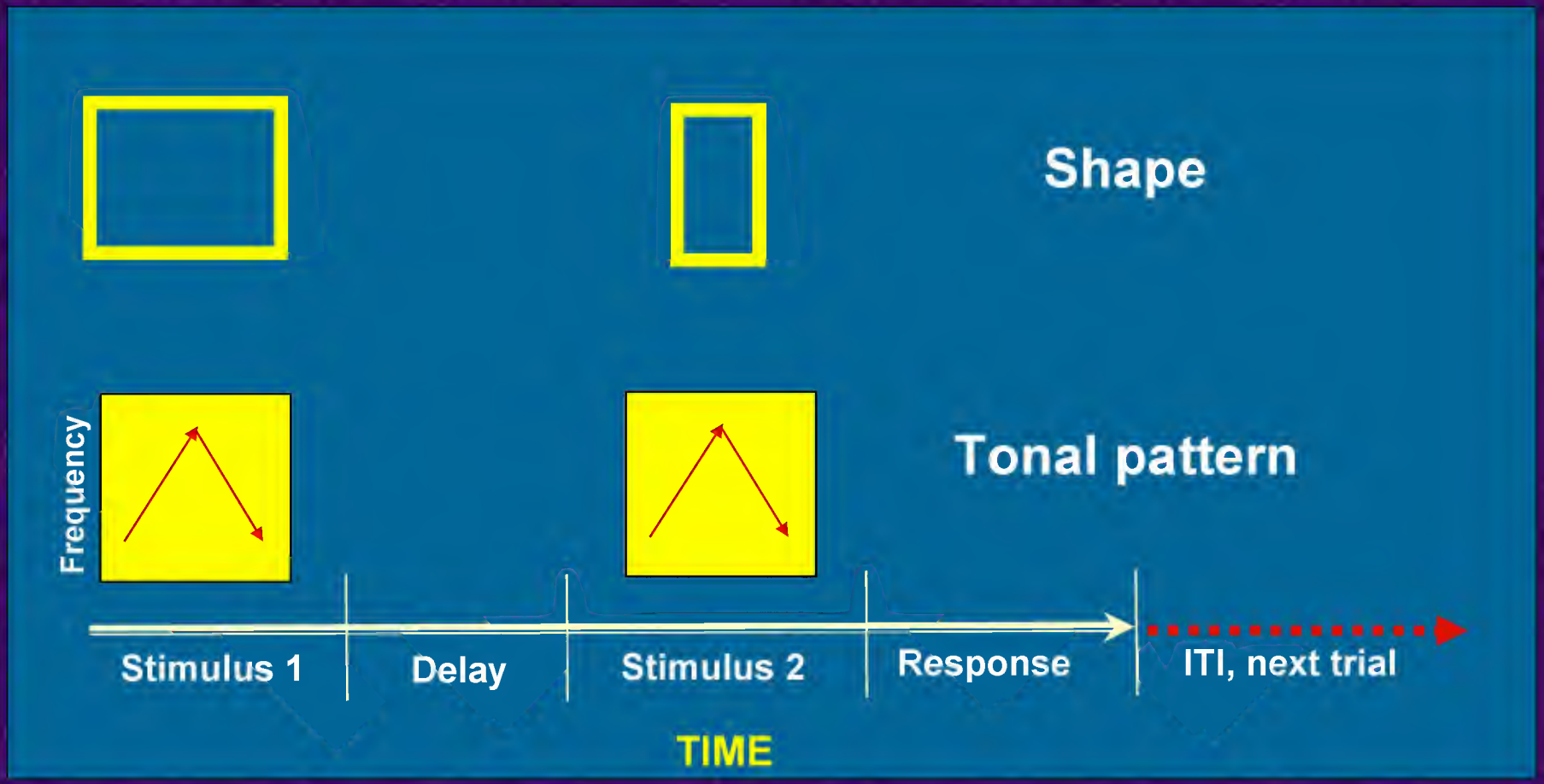
Neuroanatomy for Visual and Auditory Object Processing



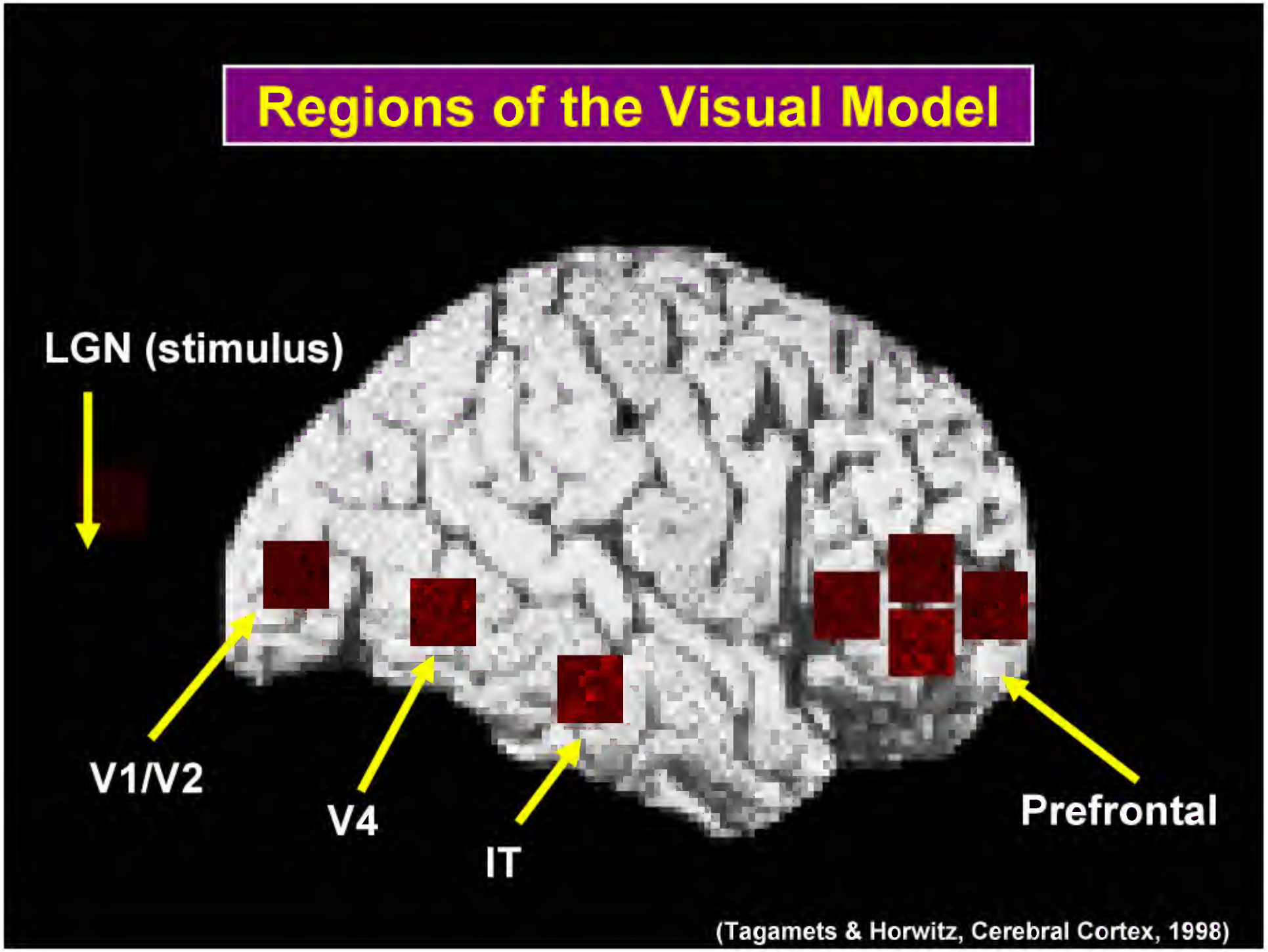


Much less is known about the neuroantomy and neurophysiology of primate auditory pathways than about the visual pathways.

Delayed Matched-to-Sample Tasks



Regions of the Visual Model



Neuronal activity in Monkey PFC During an Oculomotor Delay Task

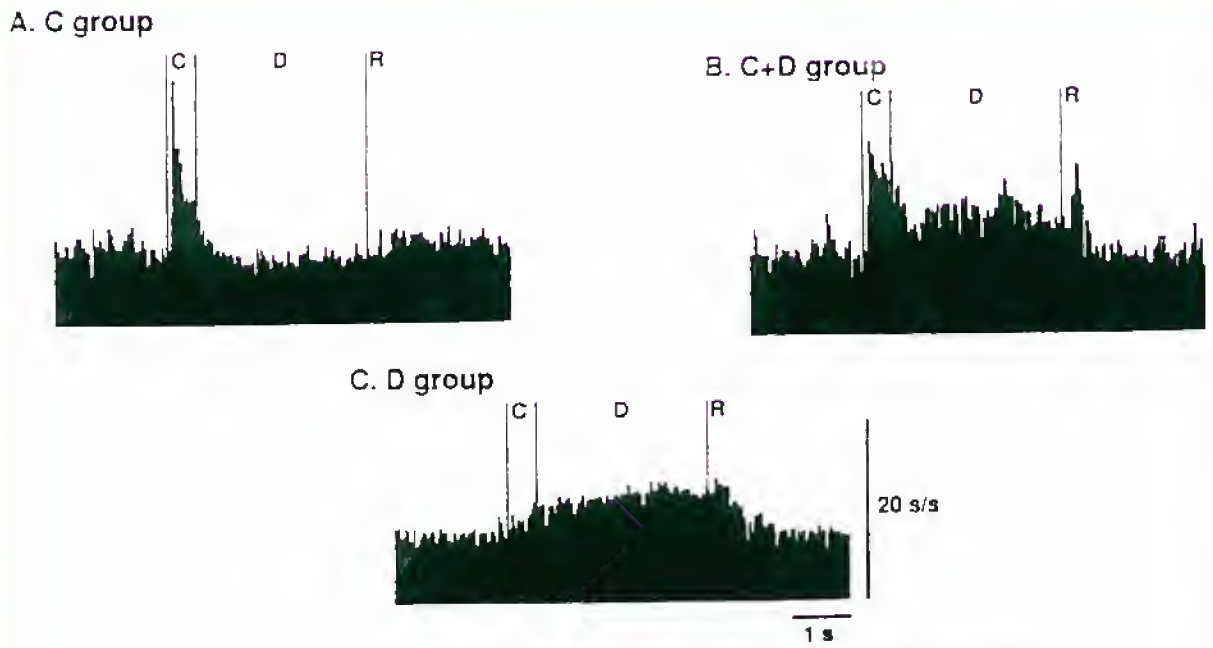
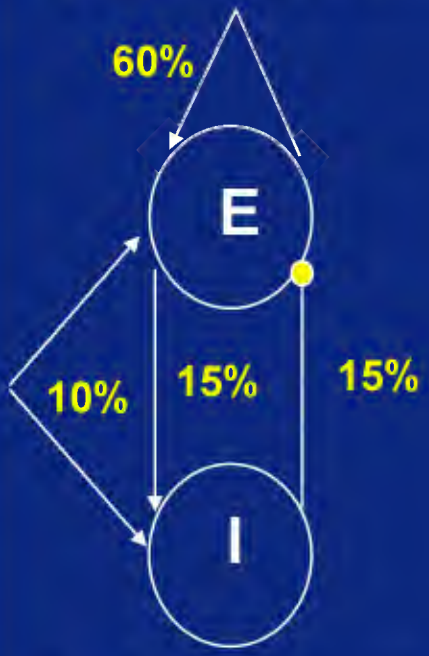


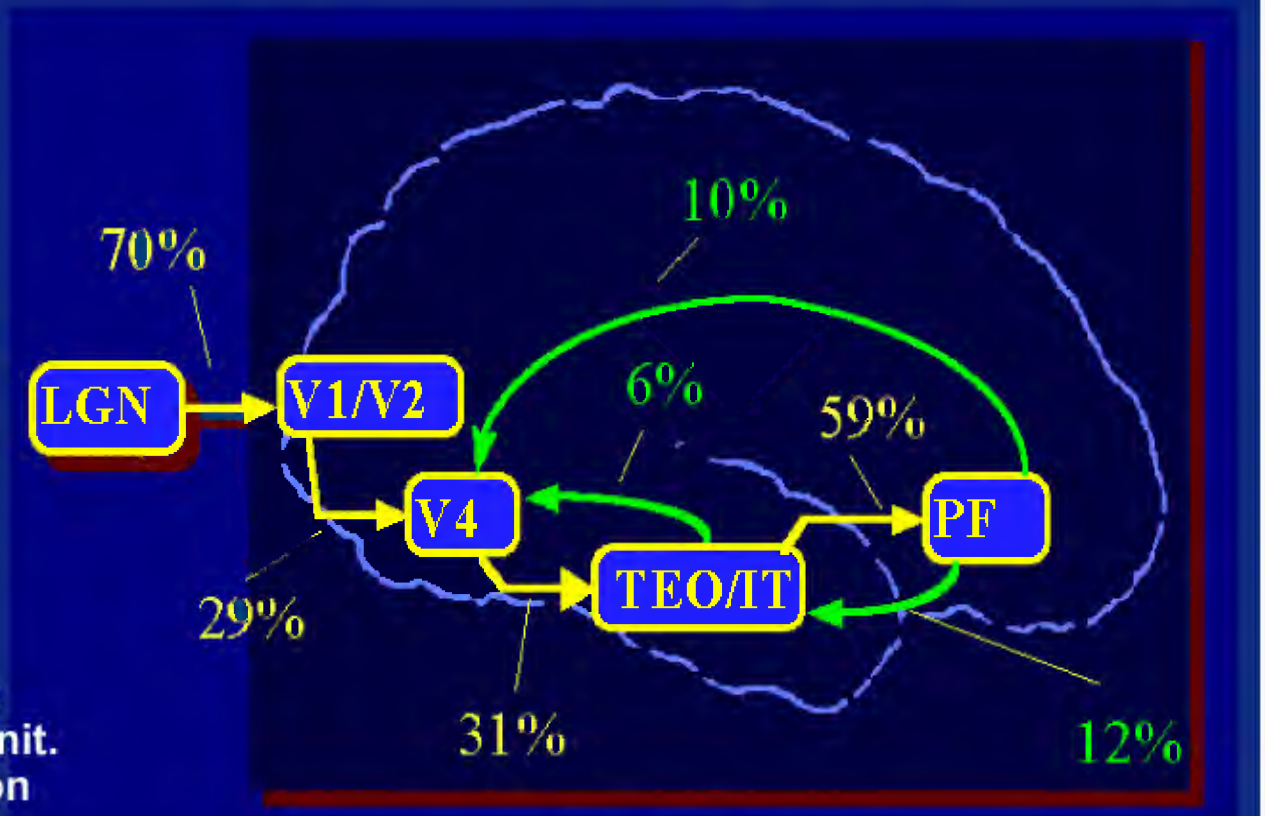
Fig. 3. Composite histograms summing over a large number of neurons recorded from the principal sulcus during the ODR task. Only trials for a neuron's preferred direction (largest response) are included. (A) Composite histogram of 27 neurons that responded to the cue. (B) Composite of 33 neurons that had both phasic cue-period activity and tonic delay-period activity. (C) Composite histogram of 78 neurons that exhibit only tonic delay-period activity. C = cue; D = delay; R = response periods. (From Funahashi et al., 1990a.)

Basic Unit of Model and Between-Area Connections

Basic Unit (Cortical column)



1. One excitatory (E) and one inhibitory (I) element per unit.
2. Local connections based on anatomical data.
3. Total afferent input ~ 10-15% local connections.
4. Sigmoidal activation rule.



Feedforward

Feedback

The Sigmoidal Activation Rule

$$\frac{dE_i(t)}{dt} = \Delta\left(\frac{1}{1+e^{-K_E\left[w_{EE}E_i(t)+w_{IE}I_i(t)+in_{iE}(t)-\tau_E+N(t)\right]}}\right)-\delta E_i(t)$$

$$\frac{dI_i(t)}{dt} = \Delta\left(\frac{1}{1+e^{-K_I\left[w_{EI}E_i(t)+in_{iI}(t)-\tau_I+N(t)\right]}}\right)-\delta I_i(t)$$

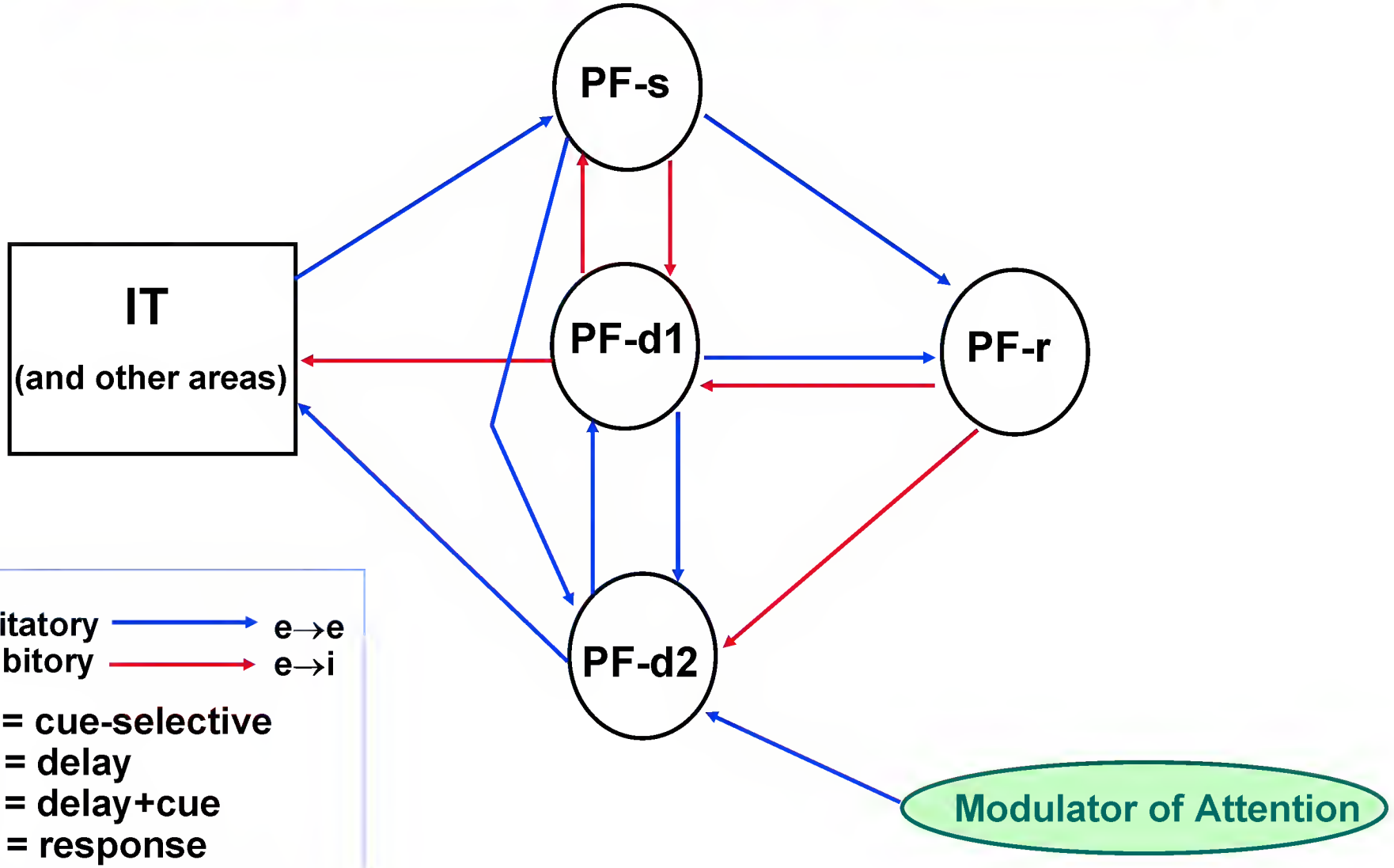
where

$$in_{iE}(t) = \sum_j w_{ji}^E E_j(t) + \sum_j w_{ji}^I I_j(t)$$

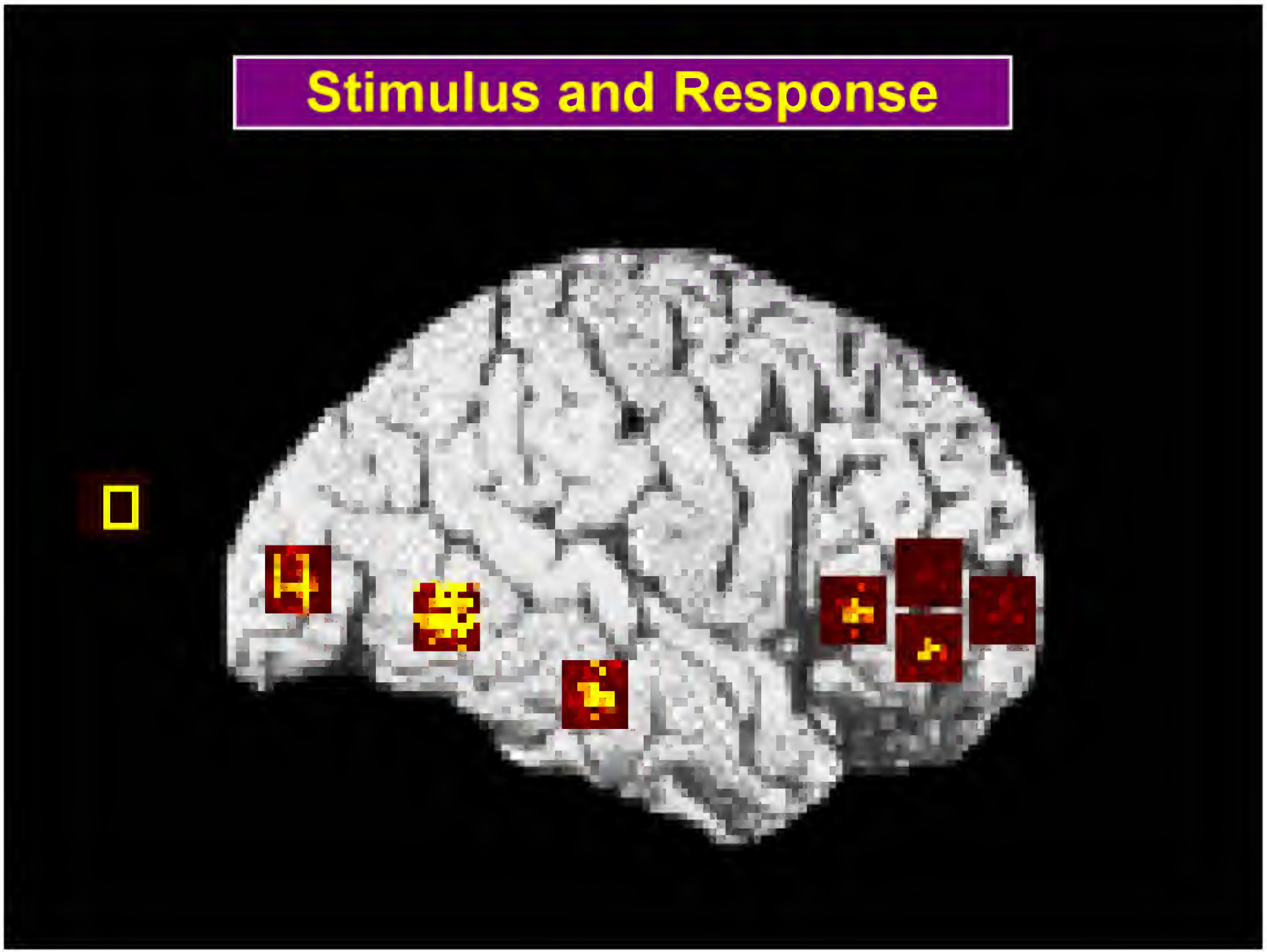
$$in_{iI}(t) = \sum_k w_{ki}^E E_k(t) + \sum_k w_{ki}^I I_k(t)$$

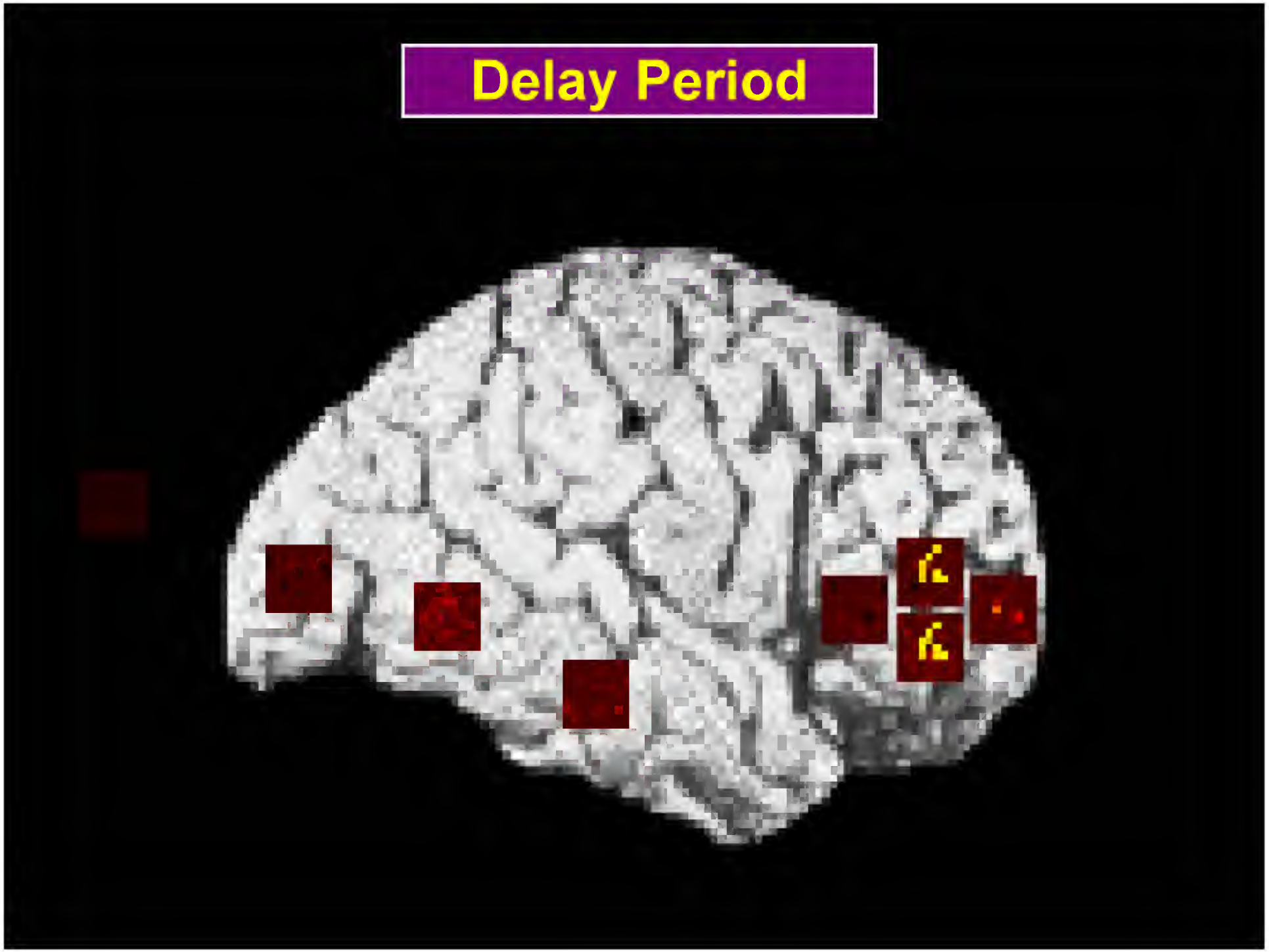
- Multiparameter differential equation
- Δ = rate of increase
- δ = rate of decay

Working Memory Module (IT-PF component)

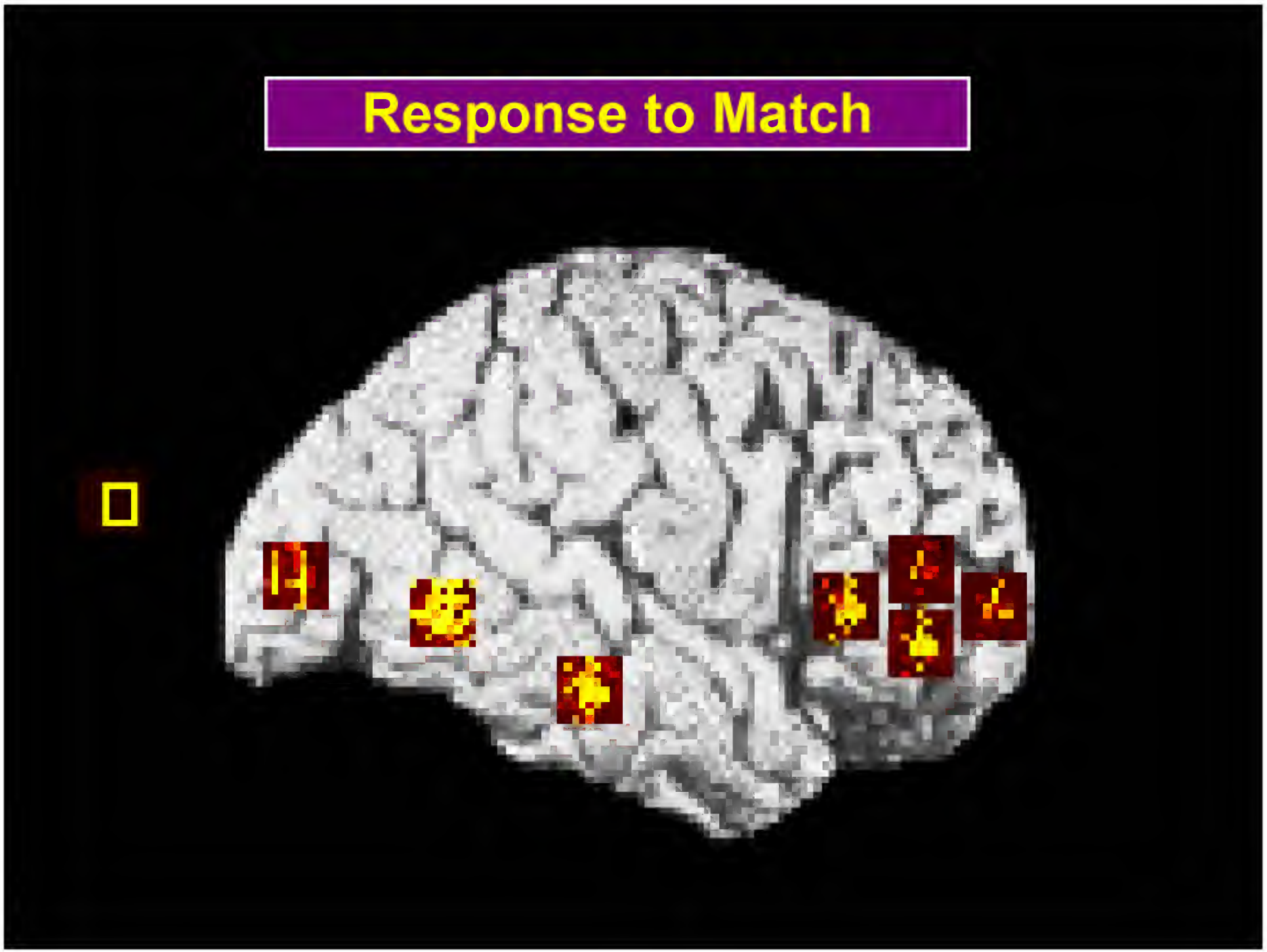


Stimulus and Response

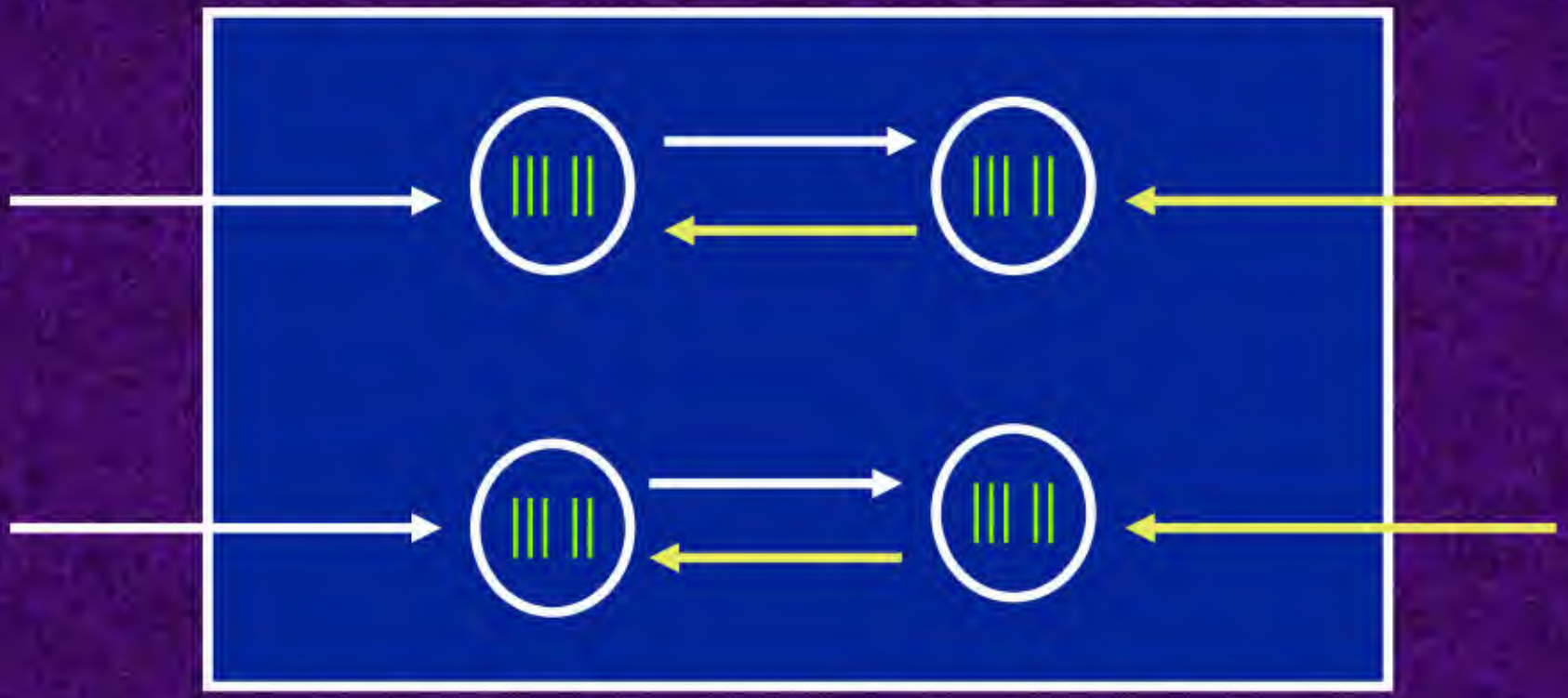



Delay Period

Response to Match



Challenge for the Model



excitatory

inhibitory

electrical activity

Results and Conclusions: Visual Model

Simulations with the Full Model

(% CHANGE WITHIN AREAS)

High Attention to Shape - Low Attention to Degraded Shape

	V1/V2	V4	IT	Prefrontal
	+3.1%	+5.2%	+2.5%	+3.5%
Experimental Results (Haxby et al., 1995)				
	+2.7%	+8.1%	+4.2%	+4.1%

Conclusions

1. Electrical activities in each region match exp. results in primates.
2. PET activities in each region match exp. results in humans.
3. Our hypothesis about how different frontal neuronal populations interact is supported.
4. Our hypothesis about relation between integrated synaptic activity and PET/fMRI data is supported.
5. Hypothesis about role of top-down processing is supported.

Simulation of fMRI Experiments

fMRI activity is simulated by spatial and temporal integration of the absolute value of the synaptic activity over 50 msec (which represents the time needed to acquire an fMRI slice).

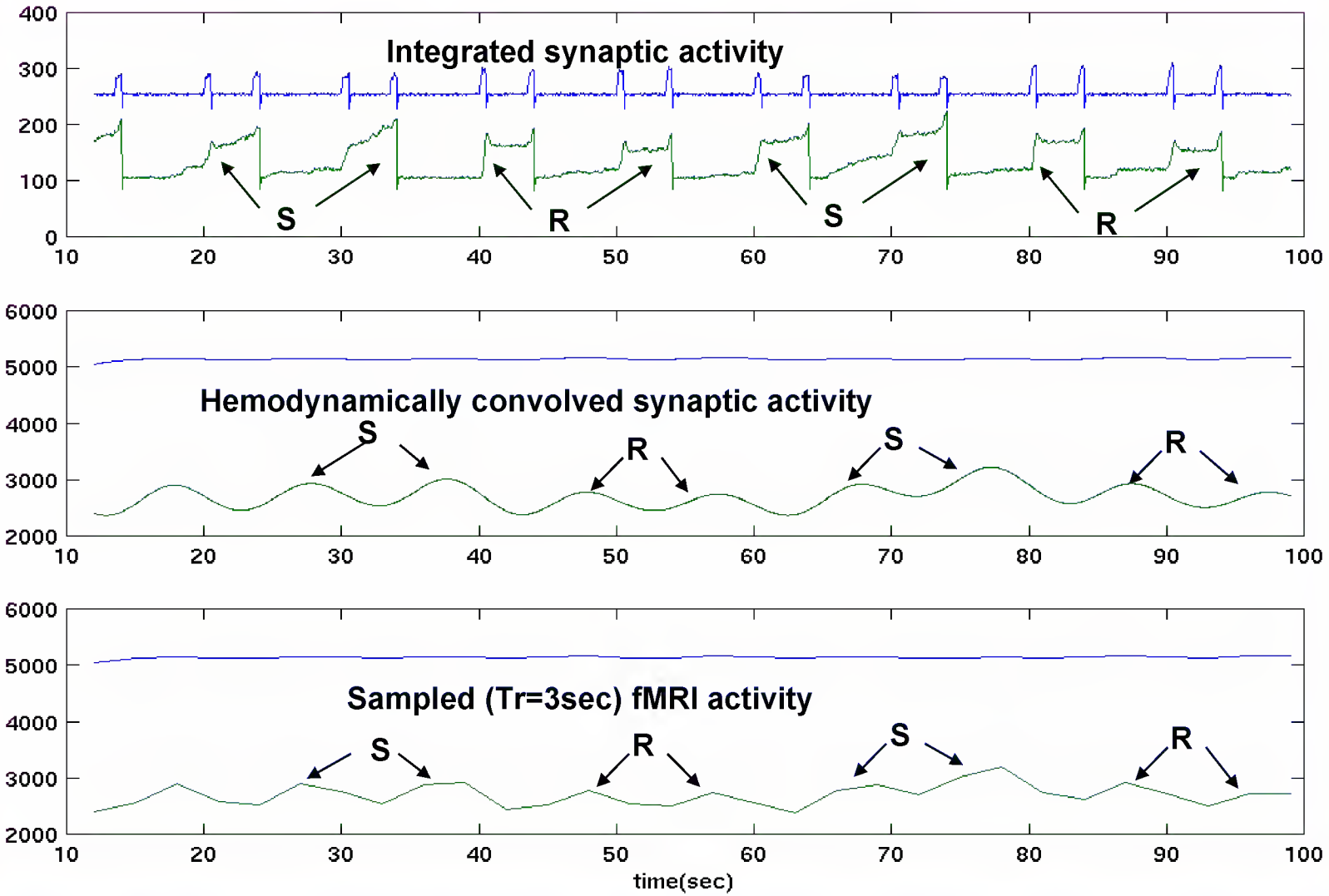
This time course is then convolved with a Poisson function representing the hemodynamic delay.

The resulting function is then sampled every Tr sec (volume acquisition time) to yield the simulated fMRI activity during each scan series.

(Horwitz and Tagamets, Human Brain Mapp., 1999)

Example: Simulated fMRI data for Auditory DMS Task

Time courses: Ai (blue) and PFC (green)

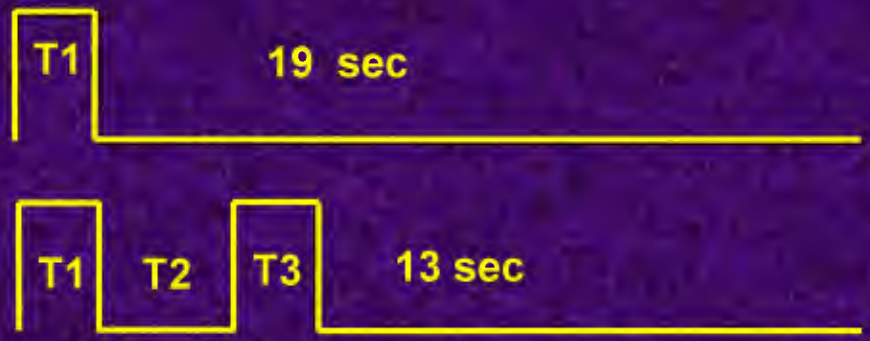


S=sweep patterns R=random tones Hemodynamic delay parameter = 6sec

Event-Related fMRI: Dale-Buckner Study

T1 = Duration of 1st stimulus
T2 = Interstimulus interval
T3 = Duration of 2nd stimulus

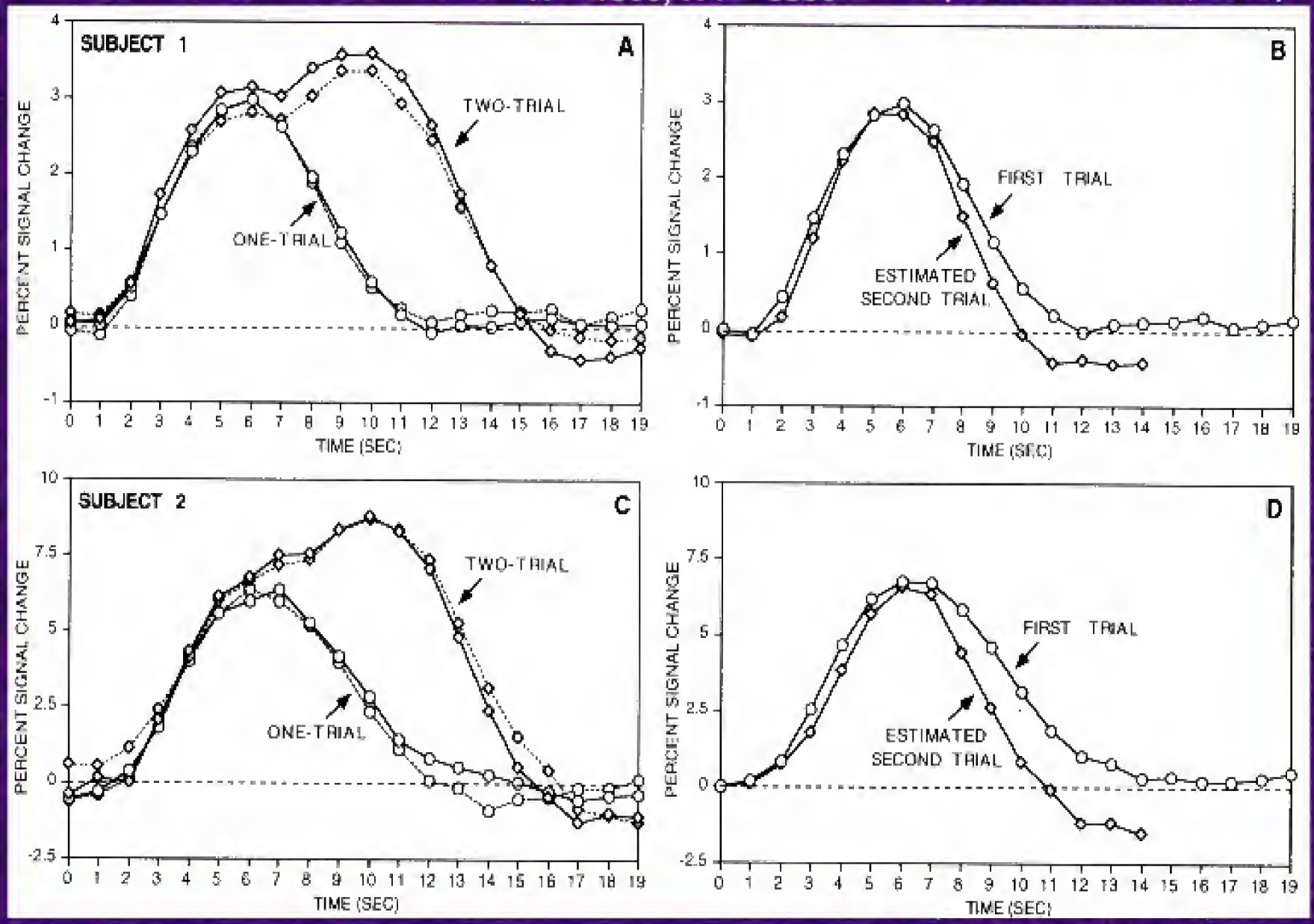
T1 = 1 sec; T2 = 5 sec; T3 = 1 sec



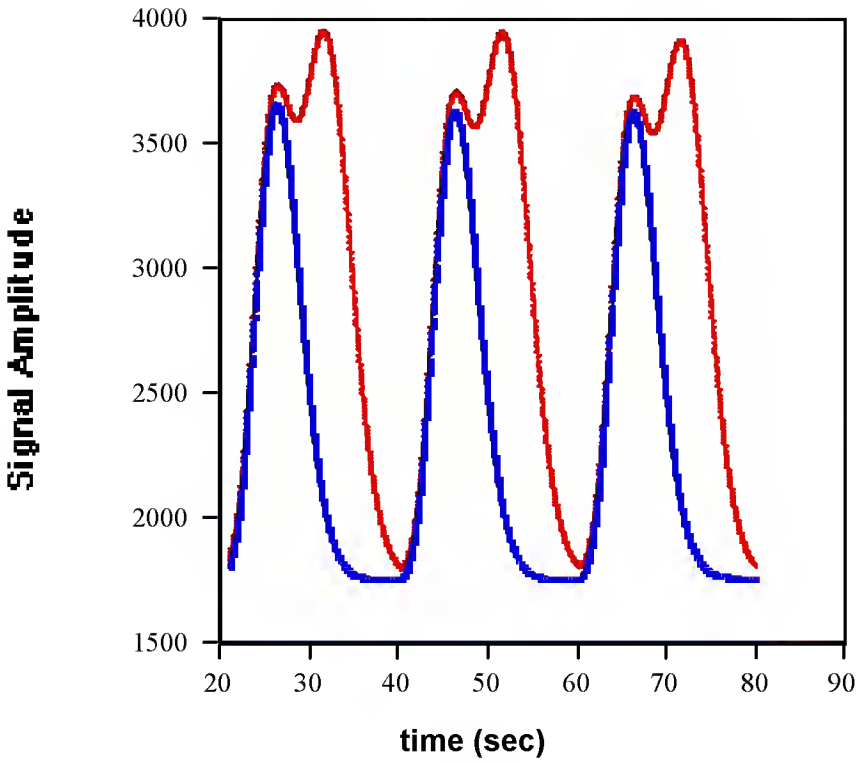
Stimuli: Flashing checkerboard (8Hz); Tr = 1 sec; hemodynamic delay parameter (λ) = 6 sec.

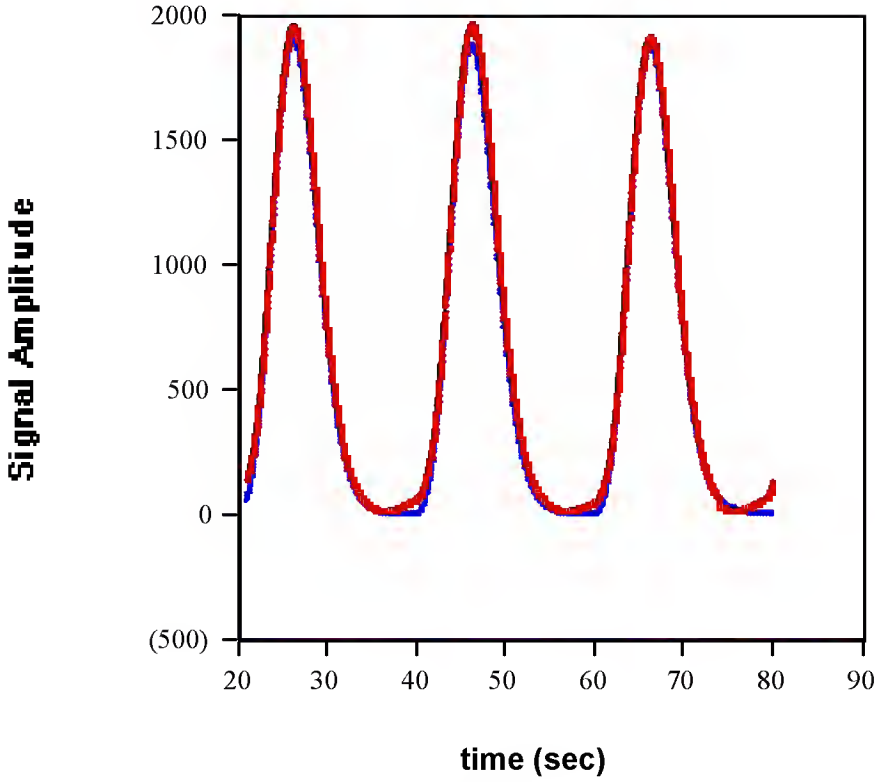
Event Related fMRI--Experimental Results

Tr = 1sec; ITT = 5sec (Dale & Buckner, 1997)



Event Related fMRI -- Simulated Results: V4



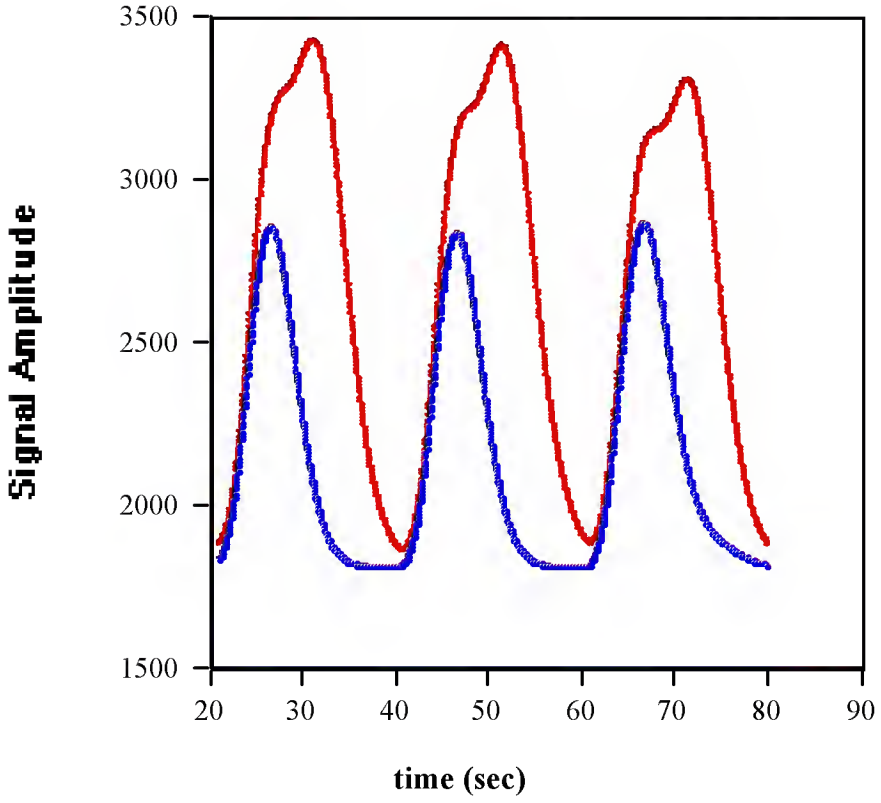


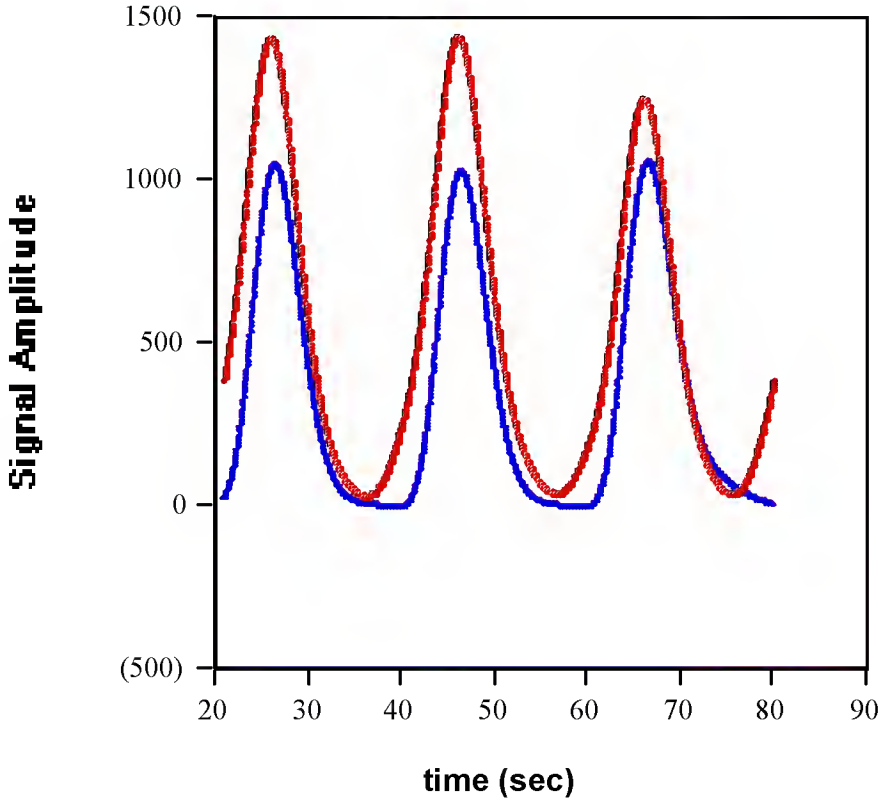
Tr = 1 sec; λ = 6 sec; delay = 5 sec

1st trial

Est. 2nd trial

Event Related fMRI -- Simulated Results: Prefrontal Cortex





Tr = 1 sec; λ = 6 sec; delay = 5 sec

1st trial

Est. 2nd trial

Conclusions
Simulation -- Event-Related fMRI

1. Simulated and experimental results are quite similar in posterior brain areas. These results provide validation for our large-scale neural model, especially its behavior during small time intervals.

2. Results of the simulation in anterior brain areas, especially the prefrontal cortex, suggest caution in interpreting event-related fMRI in brain areas where there may be substantial neural activity when stimuli are not present. In our simulation, the estimated second trial differed from the first trial due to convolving of activity when the stimulus was present with activity during the inter-stimulus interval.

Collaborators

Malle Tagamets
Fatima Husain
Antonio Ulloa
Randy McIntosh
Allen Braun
Katrin Amunts
Karl Zilles
Arun Bokde
Rhonda Friedman
Mike Glabus
Karen Berman
Theresa Long

and others

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